

Dr. Casey Halpern: Biology & Treatments for Compulsive Eating & Behaviors |
Huberman Lab Podcast #91

My guest is Casey Halpern, M.D., Chief of Stereotactic and Functional Neurosurgery and Professor of Neurosurgery at the Perelman School of Medicine at the University of Pennsylvania. Dr. Halpern's research and clinical practice focus on using deep brain stimulation to treat compulsive and movement disorders (e.g., binge eating disorders, bulimia, obsessive-compulsive disorder (OCD) and Parkinson's disease essential tremor, dystonia). We discuss using deep brain stimulation to help patients who suffer from movement and compulsive disorders and applying this treatment to patients afflicted with binge eating. We also explore applications of this technology to other conditions such as OCD, anorexia and tremor, and the future therapeutic directions of the use of non-invasive brain stimulation approaches, including transcranial magnetic stimulation and ultrasound, for the treatment of other psychiatric illnesses and conditions. This episode will interest those curious about the biology of eating, anorexia, bulimia, compulsive thoughts and behaviors, and movement.

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Dr. Casey Halpern

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Articles

Pilot study of responsive nucleus accumbens deep brain stimulation for loss-of-control eating: <https://go.nature.com/3Sc1ZA1>

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welcome to the huberman Lab podcast where we discuss science and science-based tools for everyday life I'm Andrew huberman and I'm a professor of neurobiology and Ophthalmology at Stanford school of medicine today my guest is Dr Casey Halpern Dr Halpern is the chief of neurosurgery at the University of Pennsylvania School of Medicine his laboratory focuses on bulimia binge eating disorder and other forms of obsessive-compulsive behaviors normally when we hear about eating disorders or obsessive-compulsive disorders of other kinds the conversation quickly migrates to pharmacologic interventions and serotonin or dopamine or talk therapy interventions many of which can be effective The Halpern laboratory however takes an entirely different approach while they Embrace pharmacologic and behavioral and talk therapy interventions their main focus is the development and application of engineered devices to go directly into the brain and stimulate the neurons the nerve cells that generate compulsions that cause people to want to eat more even when their stomach is full in other words they do brain surgery of various kinds sometimes removing small bits of

brain sometimes stimulating small bits of brain with electrical current and even stimulating the brain through the intact skull that is without having to drill down beneath the skull in order to alleviate and indeed sometimes cure these conditions today's discussion with Dr Halpern was an absolutely fascinating one for me because it represents the Leading Edge of what's happening in modification of brain circuits and the treatment of neurologic and psychiatric disease for instance they just recently published a paper in nature medicine one of the Premier journals out there entitled pilot study of responsive nucleus succumbings deep brain stimulation for loss of control eating the nucleus that Cummins is an area of our brains that we all have in fact we have two of them one on each side of the brain that is intimately involved in the release of dopamine for particular motivated behaviors and while most often we think about dopamine for the release of behaviors that we want to engage in in this context they are using stimulation and control of neuronal activity in nucleus accumbens to control loss of control eating something that when people suffer from it despite knowing they shouldn't eat despite not even wanting to eat they find themselves eating so again this represents really the Leading Edge of where Neuroscience is going and certainly is going to be an area of Neuroscience that's going to expand in the years to come and Dr Halpern and the members of his laboratory are among a very small group of scientists in the world that are using the types approaches that I described a minute ago and that you're going to hear more about in today's episode in order to resolve some of the most difficult and debilitating human conditions during today discussion you will also learn about the use of deep brain stimulation and other approaches for the treatment of movement disorders such as essential tremor Parkinson's disease and various types of dystonias which are challenges in generating particular types of movement so whether or not you or somebody that you know suffers from an eating disorder from obsessive-compulsive disorder or from a movement disorder today's episode is sure to teach you not only about what's happening in those Arenas but also in the Arenas of Neuroscience generally in fact I would say today's episode is especially important for anyone that wants to understand how the brain works

00:03:18 ROKA, Eight Sleep, InsideTracker

and what the future of brain modification really looks like for all of us before we begin I'd like to emphasize that this podcast is separate from my teaching and research roles at

Stanford it is however part of my desire and effort to bring zero cost to Consumer information about science and science related tools to the general public in keeping with that theme I'd like to thank the sponsors of today's podcast our first sponsor is Roca Roca makes eyeglasses and sunglasses they're of the absolute highest quality the company was founded by two All-American swimmers from Stanford and everything about Roca eyeglasses and sunglasses were created with performance in mind I've spent a lifetime working on the biology the visual system and I can tell you that your visual system has to contend with a number of very important challenges in order for you to be able to see clearly for instance when you go from a sunny area to a more shaded area and then back out again it's a very complex process Roca eyeglasses and sunglasses were built that is engineered with that sort of biology in mind and as a consequence no matter where you are wearing them and where you happen to be you always see through them with Crystal Clarity the aesthetic of Roca eyeglasses and sunglasses is also worth mentioning unlike a lot of performance eyeglasses out there which only come in the kind of cyborg variety Roca eyeglasses and sunglasses come in those varieties but they also come in varieties that you would feel very comfortable wearing out to dinner or to work or to school really anywhere that you go if you'd like to try Roca eyeglasses you can go to Roca that's roka.com and enter the code huberman to save 20 off on your first order again that's Roca roka.com and enter the code huberman at checkout today's episode is also brought To Us by eight sleep eight sleep makes mattress covers with cooling Heating and sleep tracking ability I've talked many times before on this podcast about the close relationship between temperature and your ability to stay asleep and emerge from sleep the way Aid Sleep mattress covers work is that they allow you to program the temperature of your mattress so that you can fall asleep quickly get into deep sleep stay in deep sleep and emerge from that sleep feeling especially rested by dropping the temperature of that Surface by one to three degrees at the beginning of the night dropping it a little bit further into the night and then raising the temperature towards morning because waking up requires that one to three degree re-increase in body temperature I've been sleeping on an eight-sleep mattress cover for the last six months or so now and I can assert that it is the absolute biggest Game Changer in the quality and duration of my sleep in fact I don't really like traveling as much as I used to because the eight sleep doesn't go with me and they don't seem to have them yet in airbnbs and hotels so this is also a call to action airbnbs and hotels please put eight sleep mattresses on your beds and I'll be more apt to stay in those hotels and

airbnbs with that said if you'd like to try an eight-sleep mattress cover you can go to eightsleep.com huberman check out the Pod 3 cover to save 150 at checkout again that's eightsleep.com huberman and please note that eight sleep currently ships in the USA Canada UK select countries in the EU and Australia again eightsleep.com huberman to save 150 at checkout today's episode is also brought To Us by inside tracker inside tracker is a personalized nutrition platform that analyzes data from your blood and DNA to help you better understand your body and help you reach your health goals now I've long been a believer in getting regular blood work done for the simple reason that many of the factors that impact your immediate and long-term Health can only be assessed with a quality blood test one of the major issues with the various blood tests out there is that you get information back about lipids and hormones and metabolic factors Etc but you don't know what to do with that information with inside tracker they make knowing what to do with the information you get about your biological health extremely easy they have this very easy to use dashboard and that dashboard tells you for instance what to change in your nutrition what supplements you may want or may not want to take as well as other behavioral and other types of interventions that can allow you to move those numbers related to metabolic hormone and other factors into the precise range that's optimal for your immediate and long-term Health if you'd like to try inside tracker you can go to inside-tracker.com huberman to

00:07:19 Momentous Supplements

get 20 off any of inside trackers plans again that's inside-tracker.com huberman to get 20 off on many episodes of The huberman Lab podcast we talk about supplements while supplements aren't necessary for everyone buddy many people derive tremendous benefit from them things like enhancing sleep and the depth of sleep or for enhancing focus and cognitive ability or for enhancing energy or adjusting hormone levels to Optimal range for you the huberman Lab podcast is now partnered with momentous supplements we partner with momentous for a number of important reasons first of all the quality of their ingredients is exceptional it's really Second To None second of all they ship internationally and that was important to us because a number of you reside outside of the United States third we've worked with momentous very closely to develop single ingredient formulations now this turns out to be very important because if you're going to take supplements you want to know what's working for you and what isn't and of

course you want to optimize the cost efficiency and the biological efficiency of those supplements to find the supplements we discussed on the huberman Lab podcast you can go to live momentous spelled ous live momentous.com huberman and I should just mention that the library of those supplements is constantly expanding

00:08:28 Neurosurgeon's View of the Brain, Neurosurgery Specialization

again that's livemomentis.com huberman and now for my discussion with Dr Casey Halpern Casey I should say Dr Halpern listening welcome thank you great to be here yeah it's been a long time coming we were colleagues at Stanford and then recently you moved of course to University of Pennsylvania also an incredible institution we're sorry to lose you so it was better sweet for me too Stanford's loss is upenn's gain but um let's talk about your work uh past and present as I've told the listeners already you're a neurosurgeon which I consider the astronauts of Neuroscience because you're in somewhat Uncharted Territory or very Uncharted Territory and yet Precision is everything right the margins of error are very very small so for those that aren't familiar with the differences between neurosurgery neurology Psychiatry you just educate us a bit what does a neurosurgeon do and what does fact that you're a nurse surgeon do for your view of the brain how do you think about and conceptualize the brain yeah the scope of neurosurgery is quite broad uh when I was in medical school I I was drawn to neurosurgery because of a procedure known as deep brain stimulation when I was at Penn as a college student I actually watched my first deep brain stimulation surgery performed by Gordon boltuck who to date is one of my career mentors deep brain stimulation is a one surgery that neurosurgeons offer but it's actually sort of a very small minority of what neurosurgery does you know we take out brain tumors we clip aneurysms in the brain we take care of patients that have had traumatic brain injury concussion spine surgeries ninety percent of what neurosurgeons do around the country uh you know taking care of herniated discs and lumbar fusions so you know the scope is the entire central nervous system include including the peripheral nervous system we take care of patients with carpal tunnel syndrome and nerve disorders now over the course of the past two decades or so there's been a a mission in the field to to sub-specialize and so historically neurosurgeons did everything in that domain but now we sub-specialize and I'm lucky to be at Penn Medicine where we can focus on one of these areas so I'm chief of stereotactic functional Neurosurgery all I do is deep brain

stimulation surgery and a compliment to that is focus ultrasound or transcranial Focus ultrasound which is a non-invasive way to do an ablation in the brain recently FDA approved and it's FDA approved for Trevor at the moment uh these two procedures are for me my every day but uh still the minority of what neurosurgeons have to offer the majority of neurosurgery in my mind is is a bit more structural than it is physiology or deeply rooted in how the brain functions when we take out a brain tumor we have to find a a safe trajectory to get to the brain tumor and then we remove it and we help the patient recover in the ICU similar to a brain aneurysm often we don't have to go into the brain to clip a brain aneurysm but we go around the brain or under the brain to get there and in my mind those surgeries are a bit more structural deep brain stimulation the surgery that I do routinely is a procedure where yes there is structure involved of course we have to place a a very thin wire that's insulated deep into a part of the brain that's involved in Parkinson's disease for example uh but that's actually not the therapy the therapy is delivering electrical stimulation through the tip of that wire or one of the tips as there actually are multiple contacts at the bottom of the wire they're very small uh but that's all done out of the operating room you know this stimulation wire is connected to a a battery pack or a pulse generator that's kind of like a pacemaker and so we deliver this therapy and I always tell patients it's a bit more like I have to implant a uh a tool to deliver you a medication but that medication is going to be in the form of electricity and it's going to be delivered into a very small region of the brain and it's that procedure that's inspired me to not just become a

00:13:05 Deep Brain Stimulation & Other Unexpected Positive Effects

neurosurgeon but has really defined the focus of my research laboratory as well Maybe by way of antidote you could tell us one of the more outrageous or surprising or who knows um delightful and thrilling things about the brain that you've observed as a consequence of stimulating different brain areas you know in textbooks we always hear about uh the kind of dark stuff you know stimulate one brain area somebody goes into a rage stimulate another brain area a person starts laughing uncontrollably first of all um given that some of the information let's hope not much but some of the information in textbooks is incorrect is are those sorts of statements true can one observe those in the clinic and what are some of the more interesting uh and I don't necessarily mean entertaining but um surprising things that you've seen when you've poked around in the

brain deliberately of course and uh what have you seen what have you heard I have to say I I am amazed by these effects uh every day yeah I'm very privileged to be able to interact with the human brain in this way it's always in them with the goal of trying to provide somebody with a meaningful therapy but when we deliver electrical stimulation you know the these electrodes while they might be sitting in a very small region of the brain there are regions within a few millimeters of where these electrodes are that if stimulated could cause a temporary very brief side effect a moment of laughter like you said or a moment of panic and of course we can just shut that electrode off but often these side effects could be therapeutic and actually that's how we have discovered ways to use deep brain stimulation not just for movement disorders like Parkinson's disease but for example patients with Parkinson's disease that have a psychiatric uh uh comorbidity like depression or obsessive-compulsive disorder a lot of these patients are highly compulsive and impulsive sometimes these problems actually melt away and we're trying to help their Tremor but the patients also tell us that their gambling issue has gotten better or their mood has improved and why is that well you know there's probably more than one reason you know you can help somebody's Mood by making their Tremor go away of course but we see laughter in the clinic sometimes and and why is that and that's because we're stimulating parts of the brain that are not just involved in these motor circuits but they're also involved in what we call a limbic circuit or part of the brain involved in emotion and if we learn how to modulate those areas therapeutically step by step we can actually develop these therapies for other indications like depression I would say the most impressive and consistent effect we have when we have a patient with Tremor who has been tremming for the past 20 years if we can deliver stimulation through that electrode in the clinic we have immediate relief of Tremor and that is the effect that inspired me to be a neurosurgeon when I was in college I've never really wanted to do anything else X accept help develop that type of therapeutic for another another kind of symptom I'm very interested in obesity and related Eating Disorders compulsive Behavior the urge to uh to to have something that might be delicious but dangerous or unhealthy or a drug or a compulsion like we see in OCD or pests of compulsive disorder uh interestingly like we see Tremor melt away when we deliver electricity to a certain part of the brain we can see these psychiatric more psychiatric problems they're not all psychiatric disorders but let's say disorders of the brain we can see symptoms of those disorders also improve and often immediately just like we do with Tremor so I see it all the time to to pick out one uh would be would be a challenge

because for me this is my my everyday the speed of the relief that you described for Tremor is really um incredible just thinking about drug therapies and there too there are side effects but they're still a lot of mysteries as to for instance why ssris even work when they work

00:17:20 Obsessive Compulsive Disorder (OCD), Prescriptions & Cognitive Therapies

and the timing is always a challenge timing dosage yes absolutely um I'd love to learn more from you about OCD I I have several reasons for asking this first of all I'm a somewhat obsessive person I tend to be very very narrowly focused although I confess it's not a step function it takes me some time to turn off the chatter but once I'm into a thought train or a mode of being uh and thinking and work it's very hard for me to exit that that mode it's like a deep Trench adaptive in some circumstances less adaptive than others as you know the other is that when I was a kid uh I had a little bit of a grunting tick I used to I had a this intense intense desire to clear my throat um to the point where my my dad said like you need to stop that he used to squeeze my hand every time I do it and I used to hide in the back seat of the car in the closet to do it because it provided so much relief and then it eventually passed yes I wasn't medicated they never did anything about it every once in a while now if I'm very fatigued if I've been working a lot I notice it starts to come back I'll do this like kind of grunting and so it's been sort of like a pet neurological symptom for me that reminds me that these these circuits exist in all of us and that sometimes they go haywire and sometimes they just have subtle um you know over excitation or something of that sort and then the third reason is that I get thousands of questions about OCD could you perhaps just tell us what is OCD sure um what are some brain areas involved what are the current range of treatments and what's the difference between someone who is obsessive and somebody who has true OCD so a brief disclosure as a neurosurgeon I do take care of patients with severe obsessive-compulsive disorder um but my perspective on OCD may be a little bit different than a psychiatrist who who lives and breathes OCD and sees patients every single day with OCD I'd probably take care of a three to five patients a year with deep brain stimulation for obsessive-compulsive disorders so I don't see these patients as routinely but my laboratory is geared as a researcher I'm very focused on trying to improve outcomes of deep brain stimulation for for OCD so I do feel I have expertise and and a perspective to share but just a brief disclosure I I do feel that as a neurosurgeon I am obligated to

better understand where the obsessions in the brain come from and how we can interrupt them to stop the compulsion that's associated with the obsession sort of the intrinsic most feature of OCD uh better than we're actually doing it for example if we were to offer a patient with Tremor deep brain stimulation surgery of course there's some risk to the procedure but the outcome is so consistent and positive that many patients are willing to take on that risk uh for obsessive compulsion compulsive disorder the surgery risk is about the same however the benefit is not quite as robust and so a lot of patients and they're referring psychiatrists are reluctant to refer these patients to us and it's completely understandable uh I've been leading an Endeavor with a number of collaborators around the country to try to better understand these circuits in the brain uh study them in humans both invasively and non-invasively that would be with an electrode-based surgery sort of like we do at epilepsy to understand where seizures come from we want to understand better where obsessions come from but we're also working with imaging experts and geneticists to understand OCD at a broader level as well uh I I consider OCD to be a a spectrum disorder in a way uh and I I apologize to those who who might feel that I'm using that term incorrectly I'm using it in a way to describe patients that have obsessions and even some related compulsions might not meet criteria for OCD it may be something Andrew that that you have and as a neurosurgeon I'm really obsessive about safety and compulsive about my surgical procedures so you know I I think that some aspect of OCD which we often joke about but we should you know consider seriously because people do suffer from this uh some aspect of it helps us there are you know famous uh CEOs that probably have some level of OCD uh surgeons and scientists alike so perhaps if it can be controlled it's an asset and uh but if it goes awry and is uncontrollable then it becomes obsessive-compulsive disorder and I tend to see the patients that are the most severe so they have failed medication and there are multiple medications that are worth trying for OCD some can actually be very helpful which neurotransmitter systems do they tend to poke at well ssris are sort of the the first line for OCD but also tricyclics can be helpful so this is still the serotonin system but as we know the serotonin system interacts with the you know neuroenergetic system and the dopamine system so it's hard to be specific to one of these things and I think that's also why it's hard for us to predict how these medications are going to to work for these kinds of patients but tricyclics and ssris can be very helpful and are definitely first line and there's others exposure response prevention is uh probably the most effective option which is kind of like cognitive behavioral therapy but

these are different and offered by psychologists and this is a whole field and there's a field or I should say a whole clinic at my institution focused it was started by Edna foa at Penn who this is what they do for these patients uh is offer these types of cognitive therapies exposure to the stressor and to try to get patients to habituate to whatever it is that stresses them and causes these uh compulsions to help these patients live in every day and function these are all fabulously helpful therapies for a variety of patients but there's still about 30 of patients that still suffer from OCD and some of them have severe OCD sometimes it's moderate to severe and those are the patients that I'm really motivated to try to help um our therapies for those patients right now I would say are are worth pursuing but not optimal um and so it's it's one of those things that we have to balance as a researcher because when you see patients like this you want to do everything you can to help them and I think it's important to educate patients on the risks and benefits of them this is deep brain stimulation surgery but also capsulotomy which is more of an ablation approach a little bit like deep brain stimulation but rather than delivering stimulation through an electrode you can actually heat the tissue and even destroy it some would say this part of the brain is very safe to destroy it's kind of like an appendix um others would say it's safer to modulate I have seen patients do very well with these ablations and so you know you asked me earlier what what I find so amazing about the brain these effects that we can have sometimes the lack of effect is what's so amazing you can actually Traverse parts of the brain without having any adverse effects on patients function at least that you can test but you can also destroy small parts of the brain we're talking three or four millimeters in size these little ablations can be really helpful for patients but have no obvious side effects that we can tell perhaps after a short recovery from surgery but nonetheless despite how safe they might be these surgical procedures still are surgical procedures and patients are hesitant to perceived especially when they know that their chance of a transformative effect is quite low we can generally achieve a responder rate of about 50 percent and responders still have symptomatic OCD so I'm really uh sort of inspired to really find a way to deliver these therapies in a more disease specific or symptom-specific way but we're years away probably from from that

00:25:40 Brain Areas in OCD, Risk, Rewards & Addiction

therapy since it's all part of a research study at the moment what brain areas should I

think about when I think about OCD years ago I remember opening a textbook I think it was an undergraduate still and work from Judith Rappaport at the National Institutes of mental health this would be late 80s early 90s was um had done some neuroimaging or maybe it was pet or some other Imaging technique and had identified portions of the basal ganglia sure caudi putanum type structures in OCD and maybe some differences in boys versus girls so what brain areas are there sex differences in terms of OCD and were one to come into your clinic this you know for this sort of a work of ablations or stimulation uh where would you first start to probe in the brain yeah you this is a uh a disorder of both cortex and the Sub sub cortex uh the cortical control areas areas that are involved in inhibitory control we have found to not function properly in patients with OCD so areas like the orbital frontal cortex and the prefrontal cortex if you image these areas or study them even in a a rodent model of OCD which quite honestly these models they model aspects of OCD but OCD is a human condition you can't really model this whole condition in a in a mouse or a wrap but perhaps you can model compulsive behavior in a rat sure and pulling out their hair yeah exactly you know that's that's not necessarily obsessive compulsive disorder but that is compulsive behavior and perhaps if you can ameliorate that in a rat that might be helpful for a patient with OCD but we have to approach animal modeling of OCD thoughtfully uh and and most scientists do I think uh when we study OCD in in models or in in humans with imaging and and we're trying to do it invasively with with electrodes like we do in epilepsy patients we find that areas in the cortex like the prefrontal and orbital frontal cortex are are not functioning they will the way they would in a non-oc patient they are often hyper functioning uh such that while you might say Well they're hyper functioning so aren't these patients you know functioning better that hyper focused yeah hyper focused exactly um no I I would say it's it's not so much an up or down it's more that they're just dysfunctional and we need to find a way to try to restore normal function to these areas it's not so much directional really um we tend to oversimplify brain function by thinking about it with directionality too much um unfortunately Imaging studies sometimes demonstrate activation or hypoactivation and that's where I think these kinds of things can be misconstrued but what I would call the cortical areas of OCD is that they're dysregulated and we need to find a way to try to normalize their function so uh the frontal lobe is is huge but areas of the frontal lobe that are a bit more basal like the ofc or orbital frontal cortex and the prefrontal cortex definitely consistently seem to be implicated in patients with OCD and then their projections to the subcortex this is the basal ganglia like you were saying

caudi putamen or the dorsal striatum and these are interconnected with the ventral striatum this is an area of the brain that I uh focus a lot of my energy in um this is the ventralstratum which is not limited to but includes the nucleus accumbens this is an area of the brain that we know to be involved in gating reward seeking behavior when it's perturbed it seems to gait compulsive Behavior meaning a rat will pursue a reward despite punishment despite a foot shock for example and that can be uh similar to an OCD patient they will um check their home for safety until 3 A.M in the morning and not sleep that night in a way that is similar to a rat seeking out a food reward uh despite a foot shock um doing something because of the urge but despite the risk and perhaps there is some normal judgment there we all have to take risks to function in everyday Society to be successful we have to take a risk to take care of patients with surgery there's some risk there we make a judgment call and that's not a condition that that's just normal but when our judgment is consistently sort of puts us at risk that's where we have something like OCD but OCD is also you know it's one of many conditions that suffer from these kinds of problems we tend to label them because they tend to present in a consistent way so we have patients with OCD that have hyper checking Behavior or contamination Behavior where they if they feel contaminated they'll wash their hands for hours repeatedly or if they drop their toothbrush on the floor this will lead to a compulsive behavior of cleaning a toothbrush or brushing your teeth consistently very very common symptoms that we see or signs that the patients report to us or or that we observe but you know patients with eating disorders they tend to if if they have binging disorder they'll overeat if they have bulimia they might Purge despite the risk of these things and so um addiction is is similar we we tend to drug seek if we're addicted um uh we'll we'll pay off a dealer uh in order to get our fix and despite the risk and and that type of urge despite the risk is something that I I've always been really interested in and it's a common denominator to all of these problems and if you think about these

00:31:11 AG1 (Athletic Greens)

problems I mean these are some of the most common conditions in our society today I'd like to take a quick break and acknowledge one of our sponsors athletic greens athletic greens now called ag-1 is a vitamin mineral probiotic drink that covers all of your foundational nutritional needs I've been taking athletic green since 2012 so I'm delighted that they're sponsoring the podcast the reason I started taking athletic greens and the

reason I still take athletic greens once are usually twice a day is that it gets to be in the probiotics that I need for gut health our gut is very important it's populated by gut microbiota that communicate with the brain the immune system and basically all the biological systems of our body to strongly impact our immediate and long-term health and those probiotics and athletic greens are optimal and vital for microbiotic health in addition athletic greens contains a number of adaptogens vitamins and minerals that make sure that all of my foundational nutritional needs are met and it tastes great if you'd like to try athletic greens you can go to athleticgreens.com huberman and they'll give you five free travel packs that make it really easy to mix up athletic greens while you're on the road in the car on the plane Etc and they'll give you a year's supply of vitamin d3k2 again that's athleticgreens.com huberman

00:32:27 Facial and Vocal Ticks, Stimulants, Stress & Superstition

to get the five free travel packs and the year supply of vitamin D3 K2 I really appreciate that you're building this bridge from OCD to nucleus accumbens which is of course associated with reward in various forms and we'll get to that um I'll share a personal anecdote as a as a form of question when I was in college and studying a lot I relied on caffeine as a stimulant I've never really been into drugs or alcohol I've been Lucky in that sense I don't drink and I care less if alcohol disappeared never really liked recreational drugs so I was never drawn to them however when I was in college at the time there were these little epinephrine pills that were common in a lot of sports supplements these are like pre-workout type things yes not unlike energy drinks now which I completely avoid um and I had this experience of taking one of these and drinking some coffee and of course it gave me a lift in energy these are very similar to amphetamine they were legal over the counter at the time they're now either banned or illegal I do not recommend them and I had a lot of energy but what I noticed is that my grunting tick came back and I had I made one mistake I still think of this as one mistake which was um I engage in a superstitious Behavior I knocked on wood and then somehow it felt very rewarding like it gave me some totally irrational but internally rational sense of security around I forget what I was knocking on wood about and I found that I couldn't break that knock on wood compulsion I felt I needed to knock on wood and so then I started sneaking knock on Woods like in mid-exam and studying and pretty soon I was knocking on wood often I developed a superstition and so I'm curious about the role of

superstition and compulsion in the crossover there it makes sense logically to me but I was equally shocked to learn that when I stopped taking this stimulant which I was quite happy to stop because it did make me feel too alert couldn't sleep well Etc that the Superstition went away as well and I'm guessing this has something to do with some of the reward circuitry as it's called related to stimulants again I am not encouraging anyone to take stimulants although healthy use of caffeine or safe use of caffeine might be the one universally accepted stimulant um it was really surprising to me how quickly this came on how quickly it engaged my my thinking and my behavior the obsessions and the compulsions and how quickly it turned off when I stopped taking this Sports stimulant or whatever it was I don't even remember I think it was some form of epinephrine ephedrine sure some saw epinephrine excuse me I misspoke ephedrine um is what I described sound totally outside the bounds of of uh logic or or am I imagining at all um no it did happen I'm certain it happened yeah no I don't think you're imagining it at all I you know this the grunting that you you mentioned to me you know first of all I didn't uh comment but you know that that sort of not to put a label on it but it sounds like a tick and you know ticks in in young males extremely common and they do tend to go away linking to like since I have a good friend who actually a famous neuroscientist I won't mention who it is who's worked very hard to suppress his his blinking tits and when he gets fatigued it comes back and and um he's very high functioning yes in his personal life and his professional life but but when you're talking to him and he starts doing this so you kind of start wondering like what's going on yeah yeah and it's unfortunate you know people with these problems especially as they get more severe then you get Tourette Syndrome you know it's hard to function in our society I have some friends that have Tourette I'll tell you I I'm just so inspired because there there so um they're so confident and you know people obviously notice these problems but they they just live their life and they're very successful and that's not typical um I have I have friends that I went to Penn with undergrad that had these kinds of problems and I was always just so happy and inspired by them but what's more typical is uh you know these problems cause people to lose their confidence and and not you know uh pursue you know their profession as they may have done or um things of that nature so I I think it's all related to the fact that we our brains are very vulnerable and to get back to your question about the stimulant you know I think I think your brain was very vulnerable to it you know you you sort of may have had a predisposition to it um you mentioned that you have you're a little obsessive and with the tick there maybe you have this kind of you know on the on the

mild side of the spectrum OCD um and I I probably do as well by the way so I also also have avoided drugs for that reason uh in my life I'll drink a little bit of wine here and there but that's about it um and uh but I I think most people don't avoid these things and we see these problems in relation to not just taking a stimulant but any kind of environmental exposure our own Society causes so much stress um and that's why I think we have these human conditions these are human conditions we try to model them in in animals but most animals don't have these kinds of problems you know I've heard that you can a an animal like a a monkey in the wild can have depression a monkey's version of depression but I don't think it's really typical or human depression you know and certainly it's not as prevalent as depression is in our human society I think you know we haven't evolved to manage the stresses that are in this society that we currently have and stimulants is probably one of them you know and I I suspect you are probably a little bit vulnerable um it's possible the stimulant led to an overdrive of your prefrontal and orbital frontal cortex and even brought out a little OCD Behavior related to this super uh this Superstition that you had so um no I believe that entirely and I also think you know that's why things like OCD and other kinds of psychiatric disorders tend to present themselves in college when people leave their home and they're in school and they're stressed and they're getting exposed to things that they haven't been exposed to before outside of the home and and you know their brains aren't evolved and sophisticated enough yet to help them cope with these kinds of stresses and how it manifests is in these kinds of conditions and it's I don't want to put a label on those conditions but certainly could be a psychiatric disorder but could also just be lots of anxiety it could also be the kind of problems that you had as well so um and I think the nucleus accumbens and the cortical areas that we've been discussing that that sort of send projections to these areas are are probably at least one of the main circuits involved in these kinds of things I'm relieved it's no longer present but I confess it oh I always feel it close by a long run helps so move you know being a slightly fatigued not overly fatigued but slightly fatigued seems to move out the the kind of physical compulsion but try to channel it um never taken any medication for it then here I am so I'm still still going I may call you for a referral at some point

00:39:28 Nucleus Accumbens, Reward Circuits, Eating Disorders & Obesity

but sure at this point I'm uh I'm feeling okay um let's talk about nucleus accumbens and

reward circuitry and the relationship between OCD reward addiction uh and to just give you a sense of where I'm headed with this is into the realm of a food related and eating related uh behaviors and disorders because I know you're doing some very important work there what is nucleus accumbens I know we all have one or two um one on each side of the brain what is it what roles does it play um in healthy brain behavior and in pathology yeah the nucleus accumbens is a part of the brain part of our reward circuits The Hub of the reward circuits that I've always been most fascinated in um there are scientists around the world some of the leading arguably some of the leading scientists in the world the father of addiction Neuroscience I call him um although he tells me I'm nuts Rob malenka who has studied the nucleus accumbens since the beginning of his career and who I worked with when I was at Stanford um fabulous scientist and Mentor taught me so much um taught the world so much incredible person scientist and phys and Physicians yes MD PhD and uh brilliant in both ways and um very fatherly in a lot of way in terms of teaching people how to how to do science and and be good citizens as well um but uh the nucleus accumbens is an area that is also very complicated because it has a lot of functions uh it it interconnects with many parts of the brain um but there are some things about the nucleus accumbens that are very consistent uh so when I started getting interested in reward and what a what I could do as a surgeon to try to improve how we manage Rewards and what I mean by that specifically is if you have an urge for a reward that that's a normal phenomenon that's not something we're trying to stop the issue is if you have an urge for a reward that either puts you or somebody else at risk it's probably a reward we shouldn't have I suppose you could say well it depends on the size of the reward and the size of the risk and how that fits into your societal Norms um but for example if you're obese and you have a doctor who is advising that you lose weight and try to control your eating habits uh you know perhaps better food choices is an important way for you to be healthier and and not pursuing those better food choices that's an urge that we probably need to treat uh if you're a drug addict and you use heroin or opiate considering the opiate crisis right now or cocaine which is untreatable at the moment uh you know that that cocaine might make you feel like you have some more energy that day to deal with your work or that opiate might make you feel better because life is stressful but the risk of doing those things is really high in fact potentially lethal uh so that's an urge that's treatable if you have OCD and you can't sleep at night because you're so nervous that you didn't lock the door and you've checked 30 times that's a reality for some people with severe OCD um that's an urge we

got to treat eating disorder is the same eating eating disorders and obesity are obviously linked because of the relationship of a patient with food but they're also quite distinct not everybody with obesity has an eating disorder and obviously not everybody with an eating disorder has obesity I'm particularly interested in patients that have binge eating disorder as well as obesity because they're so heavily linked but not everybody with bingeing disorder has obesity but on average most are overweight um we are doing a deep brain stimulation trial at Penn where we're trying to modulate the nucleus accumbens and understand it better in patients that have failed gastric bypass surgery the most aggressive form of treatment for obesity and we and we believe they failed gastric bypass surgery because of binge eating disorder meaning they just can't control how much they eat so their obesity is either related or even due to overeating not some predisposition to um that body habitus you know obesity is a phenotype something that we can see not everybody is obese because of the same thing so it's very important I was taught this by a close mentor and friend Tom wadden when he was the director of the Obesity Center at Penn or the center for weight eating disorders and and he said to me you know Casey uh you know be careful with obesity you're interested in addiction and I understand you're interested in the addictive Tendencies of certain patients with obesity uh uh and and their relationship with food but not everybody with obesity has that problem and and in fact it's it's probably present about 20 of patients with obesity but now taking a step back twenty percent of patients with obesity is still a massive problem of epidemic proportions and perhaps some of these patients have either some form of bingeing disorder or or I should say some degree of bingeing disorder uh or at least loss of control eating which is common to both um so that's a feature that I think eating disorder experts obesity experts neurosurgeons obesity obesity medicine experts would agree is common to eating disorders and obesity and I also believe would be common to addicts and perhaps patients with OCD is sort of a loss of control disorder um it's actually not a disorder known by like the DSM-5 some diagnostic manual but a feature I should say of these conditions that's common and that common denominator I believe can be restored or at least this problem can be ameliorated or improved upon by a better understanding and a tailored treatment to the nucleus accumbens specifically we've learned in mice that if you expose a mouse now this is just a model if you expose a mouse to high fat food not food that they would normally eat food that is like 60 fat high fat it's like butter um we've learned that if you expose them to food like that within two weeks their nucleus accumbens is not functioning like a mouse that was never exposed

to that high fat food there's aspects of it that are hyperactive I could say and there's aspects of it that are hypoactive or decreased activity but either way it's it's not functioning properly and most likely that function is predisposing continued behavior and then probably eventually leads to things like a habit that gets developed and that's a whole nother area of these kinds of problems that is very complicated and poorly understood but in any case if we just focus on the behavior at hand it seems that repeated exposure to something like high fat food a drug of abuse or any type of reward that is a really strong reward in a way it can hijack normal functioning of the nucleus accumbens so the goal of our invasive trial is to try to restore normal functioning to that nucleus accumbens uh in mice there seems to be a signal that predicts when they're going to lose control and we can use that signal to deliver a sort of a real-time therapy in the form of deep brain stimulation just a brief amount of stimulation and that actually blocks the behavior and what's interesting is over time that signal actually decreases in frequency which suggests some level of restoring normal function to that circuit in the mouse and we're trying to do that now in

00:47:18 Stimulation of Nucleus Accumbens, Continuous vs. Episodic Stimulation

a human trial fascinating where is the stimulation provided because I would imagine if one were to stimulate nucleus accumbens you would see a reinforcement of whatever Behavior coincided or preceded the stimulation so the stimulation it's a a brief delivery of stimulation anywhere between 5 and 10 seconds that is intended to just disrupt the perturbed signaling that's happening in the nucleus accumbens there are disorders like depression let's say that I would describe as a bit more of a state disorder and this is obviously oversimplified because we know that there's fluctuations in mood and depression as well so don't let me oversimplify it too much um but um but but for now let's forgive the oversimplification if we if we accept that depression is a state disorder or maybe Parkinson's disease is a state disorder recognizing that they do fluctuate uh these types of problems most likely not but not definitely most likely need a continuous therapy of some form a therapy that's consistent uh perhaps a therapy that fluctuates with the condition but nevertheless still consistent um binge eating disorder or OCD or addiction um and bingeing disorder in the context of obesity a lot of these patients are functioning quite normally every single day it's just that intermittently throughout the day there's brief interruptions in their normal functions such that they have thoughts about

food or the drug of abuse that they're really longing to have and so we want to deliver a episodic therapy delivered at the right time and only at the right time to try to interrupt the circuit aberration or the the problem at hand that is going to lead to that dangerous behavior and to kind of get the patient back on track to what they're doing um I don't necessarily think that it leads to a reinforcement it's possible we have to study that more but rather the goal is to just disrupt perhaps what is kind of Habitual um or or at least this kind of recurring problem that is happening you know people that have bingeing disorder at least at a severe level they tend to about once a day but they don't binge all day long of course they have a moment perhaps when they get home from work and they're

00:49:49 Binge Eating Disorder & Loss of Control Eating

stressed where they might have a bout of binge what constitutes a binge and I also want to know does binge eating disorder come on suddenly meaning as an entire disorder one day people wake up Suddenly they have bingeing disorder or is this you know a few too many buffets and I'm being entirely serious here you know kind of unlimited food and a circuit gets flipped or kind of starts moving into the high RPMs so to speak um so how does it come on and um I mean I'm actually surprised to hear that it's once a day I would think just hearing bingeing disorder I assume it's like OCD which it probably fluctuates across the day as well but I would have thought anytime people around food they just simply can't control their intake of food yes so so what does this look like in terms of the onset of the disorder and then what do you think underlies this once a day type of phenomena that's pretty interesting yeah so severe bingeing disorder these patients will binge about once a day it could be a couple times a day but in general it's not more than that moderate is about three to four times a week for example the reason I think that that seems surprising to you and if you think about it it is surprising but but um and I agree with you but the reason for that is is actually just in the definitions of the word and as a neurosurgeon in full disclosure as I as I mentioned you know I don't see these patients clinically I see them for research trial purposes and I try to understand the literature around eating disorders and I obviously collaborate with fabulous Eating Disorders uh uh in in these problems that are that are highly Innovative people uh but the word binge is a definition there's a definition to that word and you can't necessarily binge all day because our stomachs are not big enough um and so uh there's a limit to how much one can eat and to meet criteria for a binge you have to have a sense of loss of control you

have to eat an enormous amount of food in a brief period of time and yes generally that doesn't happen more than about once a day in a patient with severe binge eating disorder uh however they can lose control quite often and in fact perhaps even at every meal they might meet criteria for about a loss of control where they yes they may have lost control but they might not have eaten enough to constitute what we would Define as a binge um and that would be a there's no specific number to that by the way it's it's really just compared to their normal meal you know perhaps it's uh 50 of their daily calories in that one brief moment um so uh that's that's why I think it seems surprising that binges aren't happening more often than that what I would say is if we replace the term binge with loss of control eating loss of control eating Could Happen dozens of times a week um and in fact you know the patients that we're studying you know we've we've seen patients that lose control 20 30 times a week and that's probably the the term you have in mind when you're saying you're surprised that it's just one time a day and it's specifically related to the fact that these patients have to eat such a large amount of food in such a brief period of time

00:53:02 Developing Binge Eating Disorder: Predisposition, Environment, Stress

um so it's hard to do that more than once a day I see um you mentioned that some pre-existing anxiety might bias somebody to have a binge I'm also fascinated by something I've observed before which was when I was in college my my girlfriend had a roommate who we were aware was bulimic and would binge and then Purge and often uh when she ingested alcohol that would lead to a binge sure which is kind of the opposite of anxiety when I think about alcohol as something that slightly reduces prefrontal activity somewhat of a sedative or certainly a set of higher dosages so this brings to something that you said I'm just gonna I won't say it as eloquently as you did that it seems like it's not neither the case that anxiety leads to bingeing nor that hypo reduced activation of the forebrain and lower anxiety leads to bingeing it's this dysregulation of circuitry that the the Seesaw could go either way and it can throw things off it's off balance in both cases yes uh it's uh and that seems to be a that seems to pose a problem it seems like it's a particularly tricky problem and kind of explains to me in my non-clinical awareness why medication might be really hard to use as a way to treat this but that being able to poke around in the brain and assay in real time you know how do you feel do you feel like bingeing now or do you feel um further from the binge impulse is that what you do with

these patients are they awake while you're stimulating the brain because it's one thing to say I stimulate a brain area and the bingeing goes away or partial relief or complete relief but how do you know are they in there with a donut um and you're tempting them so how do you actually know if it's ablating a brain area is going to lead to uh relief or exacerbation or no impact on on this disorder yeah so uh there's a lot to unpack there um I'll try to go one step at a time and if I miss something please remember no and I tend to ask these three-part questions specifically of neurosurgeons because I like to challenge you guys because again you are the astronauts of Neuroscience also I'm just going to take a moment to poke at neurosurgery because I have a couple close friends um who are neurosurgeons and I consider Casey Randy I don't know if he considers me a friend but of course I am a friend I'm teasing there too which is first of all they all have incredible hands right they have I'm not they all guard their hands with the kind of um uh protection that you would guard the the tools of the most important tools of your trade so they're very careful with their hands you're not going to see them doing heavy deadlifts you're not because of the way that impacts the motor neurons it's all about fine control yes um so if your neurosurgeon does heavy deadlifts you might want to consider getting a different neurosurgery I hope I didn't put anyone out of work there and then the other the other thing is that um you all tend to be very calm people at least on the exterior we'll return to this later okay um but I do throw three or four questions out at once so so elevated autonomic arousal and alertness as well as decrease autonomic arousal and alertness both seem to be able to lead to bingeing and then there's this question of how do you know whether or not to stimulate or to ablate or whether or not to leave a structure alone in other words what does one of these experiments look like in the laboratory yeah sort of a clinic excuse me yeah of course yeah these are questions I think about all the time um and um I do want to come back to the deadlifting comment but I um regarding and you and you referred to this earlier as well and I don't know if I've addressed it sufficiently either is is sort of like what what comes first here or how does this develop um I I think first of all I I like to understand these kinds of problems in in sort of the the construct of what I I consider to be a bit of a two-hit hypothesis um so you sort of need like in the concussion literature you need the second hit is can be devastating so if you have a concussion you know you want to only return to play when your symptoms are gone uh and cleared by a physician um so uh in the context of Eating Disorders or let's say binge eating disorder first of all I I didn't mention earlier but this is the most common eating disorder affects anywhere between three and five percent of the

population wow um and it's probably under-diagnosed in obesity by the way and if obesity affects 35 of our population most likely bingeing disorder affects more than three to five percent but that's that's the current uh literature uh estimate on on the prevalence so um how do we develop a gene disorder and is it related to this anxiety question um you know I think that there is a predisposition that's the first hit um I actually think all humans have this predisposition just some have it more than others um I don't think that we've evolved to live in a society where foods are so readily available and enormously delicious and have so much sugar and fat in them not that there's any particular problem with either of these macronutrients it's just the excess of it and how they're refined uh that I think is the problem um you know those high fructose corn syrup in almost everything we eat we it's in bread I don't even know why it's in bread sometimes it's just kind of crazy so so I don't I don't think we're evolved to live in a society um that that has food that's so readily available like that um and cheap by the way in fact the cheaper the foods are sort of the the more refined and palatable and I would argue dangerous to eat I think they change our reward circuits for the worse um and put us at risk for wanting more um I tend to get a headache when I eat food like that and and perhaps that's uh evolutionary Advantage because I don't want to eat those Foods because they actually do make me sick um so um in a lot of ways I kind of wish that headache on everybody because perhaps we wouldn't have all these problems uh or at least some of them would go away so I think that's the first issue is a predisposition to uh or a vulnerability to these types of foods um which we undoubtedly all have to a certain extent but some more than others and then and then and that's so that's the first hit is this predisposition in the context of this sort of food focused Society and then the second hit is probably a stressful event or a stressful life um and probably a recurring stressful event I'm not sure this is published I've never sat down with like a eating disorder expert and and had this question about how this develops and I'm not sure it's actually well well known um but in a lot of ways I think that that answer anybody would agree with that we need sort of a predisposition in the exposure the environmental exposure and the genetic predisposition um but also a stressor and that stressor is probably one that's recurring and you know it's obvious in our society these stressors are everywhere and how we can manage them is is often poor and you know I think we can all relate with that and then there's something else in the background that I think is really important to mention is that patients with these kinds of problems are embarrassed because our society doesn't think fondly of these kinds of patients you know bingeing disorder patients they do tend to be

overweight that's obviously a stigma obese obesity is another stigma then there's the opposite in a way it's an opposite by the way for a phenotype standpoint is that anorexia I mean that's another stigma and you know gosh you know not to make this about one sex over another but when when girls are told they're pretty because they're thin it just reinforces this problem and of course you want to complement people and make them feel good about themselves but the problem is that in this vulnerable society that that can lead to problems because people start thinking oh I should be thin or thinner um so I think that it's a little bit of a societal understanding that our brains are very vulnerable and I think that will really help changing Society is hard and most of society is not you know ill meaning uh it's all done by accident um but that is the society that we live in so if we can try to improve that stigma uh and and be kinder to people in that way I think a lot of these problems would get better people that are obese that feel embarrassed by their obesity it doesn't help it only makes it worse because they give up same thing might be true for anorexics so I really think it's important to consider all of these things and that's why it's so complicated and it would be so hard to do a well-controlled study to understand it better because there's so many of these variables to control for that you really can't control for you might be able to control for them in a mouse's home cage but not not in the society that we live in so so that that's kind of my brief uh sort

01:02:07 Electrodes in Nucleus Accumbens, Identifying "Craving Cells"

of summary of how I would answer your first question then I think you know your second question I I sort of take that as well how do you study such a complicated problem in the operating room and and in the clinic because I mentioned the operating room because that's sort of the first step here first we want to we have uh just to clarify we have a nih-funded uh trial approved by the FDA for for research to do this first in human study um we've treated two patients we have four more to come at Penn in um and in this study uh it's something I've been working towards my entire career what we don't know is where in the nucleus accumbens will we identify cells or regions that seem to be uh involved in this sort of reward seeking Behavior I would call it a peditive it's kind of like appetite but the word repetitive is I think a a good word to use what part of the nucleus Cummins is repetitive is the whole thing repetitive probably not it's huge in my world it's huge as a neurosurgeon you know I Target parts of the brain that are three or four millimeters in size the nucleus accumbens is almost a centimeter in size wow I didn't realize it was that

large yeah it sort of like reminds me of discussions around the amygdala everyone thinks amygdala fear but Miguel has got a lot of different sub-regions and stimulation of certain areas of the amygdala makes people feel great that's right another stimulation of other areas makes them feel terribly afraid exactly and that shouldn't surprise us because you know when we treat patients with Parkinson's disease for Tremor you know if we're in one part of the subthalamic nucleus will help their Tremor if we're in another part of the subthalamic nucleus the neurologist is looking at me like why isn't this working and that shouldn't surprise us we already know that you know two or three millimeters deviation or two or three millimeters away from where we want to be and you might not have the result you want and that's probably also true for these more limbic structures like the amygdala and the nucleus accumbens uh so you know regarding the nucleus accumbens we traverse some of the nucleus accumbens not all of it in order to place the electrode that we want to use to detect when Cravings are happening for example and to try to block the Cravings from leading to the behavior related to the reward seeking which is the overeating in this case uh so what we decided to do in the operating room was to actually try to leverage a tool that we use all the time when we take care of patients with Parkinson's so with Parkinson's these a lot of these patients not all have Tremor and so when we place an electrode into this motor structure to try to improve their movement disorder we often can hear Tremor cells and they sound we convert their electrical signal to an audible signal so we can actually hear it um and it sounds kind of like the Tremor looks like the frequency of the signal is the same as the handshaking exactly and so the patient with Parkinson's is is Trump trembling Yep they're awake and you're poking around in a in a dedicated careful way of course one poke at a time one poke at a time with a very fine wire a set of wires listening to the electrical activity until you encounter some cells that are sending out electrical activity that's right at a similar frequency exactly and then you can stimulate them or quiet them and see if the Tremor goes away so we are very confident that when we stimulate that area of in this case the subthalamic nucleus uh we will make that Tremor we will disrupt that Tremor circuit and that Tremor will dissolve and it does that's why Parkinson's is so beautiful and inspiring and uh from us retractable yeah exactly but what is the it makes us feel we understand the brain right at least in that limited way so what is the um analog to Tremor in terms of appetite and desire to binge craving so craving is a term that you know there's probably other terms we could use by the way but that that's the term we've chosen to use for a number of reasons one because

people relate with that term people that have binge eating disorder or obesity they if you ask them if they crave the answer will often be yes um if you ask them if they lose control or binge they might not know what you mean or they might not actually feel out of control even when they are um so uh but the word craving is relatable and so we set out to see if we could identify craving cells um in a patient with OCD which is related in fact we target a very similar part of the brain we tried to identify cells related to obsessions and we believe we did do that it was a single case study uh where we tried to optimize where our electrode was placed so we had some proof of concept that we would be able to elicit a sort of disease-specific symptom in the operating room assuming the patient could tolerate being awake not everybody needs to be awake for this procedure but at least for these first and human trials where um we're trying we're trying to establish where in the brain we need to be uh I think this type of approach is really critical and you know by the way none of this has been published uh but I think it's so important for people to know this so I I am willing to share some aspects of what we're trying to do um but uh but that's that's really the first goal of this trial is to identify where the nucleus accumbens we can detect these craving cells so we have to provoke food craving in the operating room that's the first thing how do you do that ah well um there are some uh somewhat validated ways to do that so for example we asked patients to provide pictures of food that they rate very highly as something that they would typically crave and you know depending on the patient it might be something that's very salty it could be very sweet like a donut um oh that's very good I love donuts right Donuts are great you should you should try the Cronut when you're here in New York City I just might I try not to eat that sort of thing for all the reasons just try to stop yourself after that one so if I were one of these patients given the fact that uh the binges come on pretty seldom once a day do you you I imagine you have them come to the the operating room fasted or semi-fasted they're faster okay they're fasted which probably they're probably surgical reasons for wanting that too they kind of have to be right and then you they've you've done the craniotomy removed a patch of skull yes you've lowered the wire into the nucleus accumbens and then they are viewing pictures of food that they crave and thinking of about it do they have olfactory cues smells of cronuts yeah I would love to do the olfactory because we haven't implemented that but that is a great uh thank you for and I'll give you full credit when we do review the grant but it sounds I'm so glad this work is funded because I mean this is what I I'll make this time it's not a joke when I refer to you all uh you neurosurgeons uh as the astronauts of the brain you know this is out on

the extreme edge of what we don't know about how the brain functions and this is so far and away different than giving a mouse access to a high high fat food not that I'm not being disparaging in the mouse work but so the person says well I'm the patient in this case so I might say you know I'm hungry a donut sounds really good right now but craving to me is like I you know I'll cross the street cross town be late for my meeting eat three of these yes maybe even hide that from somebody that cares about me that doesn't want me doing this this kind of thing hide it from myself yes these kinds of behaviors I'm projecting and I'm fortunate that um I I have cravings for things in life but uh Donuts are not among the more extreme of them so um so this is all happening in real time and you're listening to the cells the same way you would listen to it and search for Tremor cells exactly same exact tools and you're doing that by um recording from a small population of cells in the area yeah in fact we do get multi-unit activity which is multiple cells uh but we really try to find one a single unit to listen to one neuron yeah because it's just um much easier to understand what that one neuron is doing versus trying to listen to and we also measure local field potential recordings but those are analyzed which is more of a population response thousands of cells kind of a porous of cells exactly um that we measure offline um the device that we use to um sort of treat these patients or intervene uh that we're studying it can't do single unit recordings it's only doing these more population responses so we correlate what we see in the operating room at the single unit level to the population response but we do that all offline um I can explain that in a moment uh but yes so we we try to identify these craving cells and uh because this is a feasibility study um and we can't you know be in the operating I'm searching for hours and hours and hours we do have some sort of we have guidelines that we've set for ourselves that we've uh developed with the NIH or the FDA to make sure that what we're doing is feasible and safe as well um so we we will spend a limited time

01:11:41 Effects of Stimulation, Interrupting Craving, Intermediate Stimulation

trying to identify these uh craving cells but another uh sort of um strategy that we think is really important is um the effect of the stimulation so a lot of patients and this gets to sort of your question earlier about what kind of what comes first um you know a lot of people when they when they binge or they lose control over food um or seek drugs that moment of vulnerability is preceded by what we call a a moment of sort of pre-meal negative

effect which basically means right before they binge they're feeling down or they feel stressed or anxious and they compensate for that momentary symptom by bingeing or losing control over food not everybody needs criteria for a binge so I try to specify that we are we are looking at loss of control eating specifically just because the Criterion of a binge is not as critical for us um so um so what we want to be able to do is trigger stimulation when this craving is detected by the device uh but we trigger it only when the craving is there and we believe that if we can sort of temporarily Elevate their mood ever so briefly again this is about five to ten seconds of stimulation only that perhaps that elevation in mood could actually sort of disrupt the craving to binge cycle maybe that's a habit maybe it's not but if you crave and then you binge if we can interrupt that with this moment of feeling good that might be a really good therapy for a patient and in fact when we do deep brain stimulation for obsessive-compulsive disorder we can fairly reliably induce a positive affect the problem is that it's not sustained and the reason it's likely not sustained is because with obsessive-compulsive disorder we treat that condition with continuous stimulation and it's not surprising that over time the effect kind of goes away so when they're in the clinic and we turn the device on our patients feel great and we feel like we've solved the problem but they call us the next day and they're like you know my my depression came back or my OCD hasn't gotten better and my moods back to where it was can you can you get it back to where it was yesterday because that felt great the brain loves homeostatic regulation it does and it does not like to shift patterns regression to the norm right um and I think there's sort of a tolerance effect there um that uh is limiting the effect of continuous stimulation and actually in a mouse if you do continuous stimulation um the the sort of blockade of binge eating goes away so actually in a mouse we've actually demonstrated um we published this not too long ago in pnas that if you deliver stimulation intermittently and only when sort of a craving signal is detected so to speak um that that X that effect will be the most robust and durable um but if you deliver it continuously actually the benefit goes away over time so I've always encouraged my colleagues to consider more of an episodic stimulation approach rather than continuous deep brain stimulation but of course that that's for these more episodic conditions whereas these more quote unquote State disorders uh as I oversimplified earlier they might need more of a continuous therapy so that's definitely subject for a lot of research in the future um so in any case um the goal in the operating room was to identify a craving cell um deliver stimulation safely but also to capture a moment of elevated mood we were able uh to do that as we we are in our OCD patients as well and also to get an

interoperative CAT scan we have devices now in the operating room that allow us to get Imaging in real time they're fabulous tools that we didn't have 10 years ago so we can confirm accuracy um you know where the you can see where the electrode is exactly precisely exactly um you know with 0.5 millimeters of air so super precise uh or as precise as we think we need to be um and we use connectomics so there's a tool in brain Imaging called tractography where we can actually measure circuit connections it's it's an indirect assay but we believe it's powerful it has its uh assumptions but um like anything in in science but we could actually map out where the nucleus accumbens connects to the prefrontal cortex sort of the cortical control inhibitory control pathway and where that pathway intersects with the nucleus accumbens and we can Target that area um structurally so those three goals of the surgery we we aim to set up to accomplish and we believed if we achieved two of those three that we would have a successful result in our in

01:16:46 Anorexia, Obesity & Compulsions, Potential Treatments for Anorexia

our early trial amazing given that at least to me the non-clination that anorexia is the mirror image of binge eating disorder and at least from what I learned one of the more deadly psychiatric conditions yeah um but also quite common yes um is it possible that nucleus accumbens this so-called reward circuit is also involved in anorexia but somehow it is the resistance to eating the craving of the fasted state or something like that that's being reinforced and and I asked this for two reasons one because I'm genuinely curious about anorexia of observed anorexia in a number of people that I know and it's a striking thing to see somebody just resist food despite all better knowledge of the fact that they're getting quite ill maybe even at risk of death but the other reason is that if in fact nucleus accumbens is the site which can Harbor cells to promote craving and craving of fasted States so to speak then that I think might tell us something fundamental about how the brain works which is that structures don't control functions per se structures control dynamics of interactions sort of like a Orchestra conductor has a certain number of operations that they perform but really their main function is to coordinate the actions of a lot of things not to make sure that the violins always play in a certain way alongside the oboes you can tell I'm not a musician here I actually have an appreciation for the openings yes those usually get left out what's that the obos yeah they usually get ignored my partner plays the elbows oh yeah so yeah I

think it's a great analogy by the way um you know I I make this statement it's a little controversial but I actually think people would understand where it's where I'm coming from um across all of these sort of sub-specialties of medicine uh but I actually think especially with obesity remember it's a phenotype that's reflective uh often but not always of a behavior um but if you consider patients that have obesity and they they exhibit some sort of compulsion towards food so they they overeat despite the risk of it I think those kinds of patients are more similar to anorexics than they are different um anorexia and obesity are both phenotypes that are at least in this specific case of obesity and in anorexia a result of a compulsion to either over or under eat despite the risk these types of compulsions are driven by societal pressures brain vulnerabilities that are probably more similar than they are different they just happen to manifest differently why they manifest differently is probably related to each predisposition or perhaps preference that's hard to know like you I have a personal connection to these Eating Disorders anorexia included and uh yeah I think it's um it's very scary and it's a condition that often instills fear in psychiatrists because I think you know not not everybody by the way I mean I have some phenomenal psychiatrists that I work with both at Stanford and at Penn they're also involved in my obesity study that take care of these patients I mean these are heroes but there's a lot of psychiatrists that are not in this domain that find anorexia scary for the reason you said it has the highest mortality of all psychiatric conditions that includes depression because not only can these patients die of suicide but they die of metabolic complications of being underweight um so it's a uh it is it is a scary condition I I relate with that I am trying over time to bridge what I'm doing in obesity and bingeing disorder to atorexia for two reasons one because I think these problems are more similar than they are different and two because of the need um and I think we're well positioned to sort of tackle anorexia um using similar approaches not identical but but similar approaches um the nucleus accumbens has been studied in patients with anorexia in China actually my postdoc my first postdoc who I had the honor to train uh when I was at Stanford as a neurosurgeon in China when before he came to me actually was involved in a trial of anorexia that had some benefits um and uh there's studies in Europe um and elsewhere that have examined preliminarily uh the effects of deep brain stimulation targeting the nucleus accumbens uh for anorexia colleagues of mine in Canada Andres lozado is a wonderful neurosurgeon scientist has been studying the effects of going after Area 25 which is directly connected to the nucleus accumbens by um you know it's a monosynaptic connection so in a lot of ways you know perhaps

delivering stimulation there could be very similar to delivering stimulation with nucleus accumbens it's all part of one critical inhibitory control circuit he's seen benefits as well um so I I definitely think there's some evidence that this is an area that we need to be studying um I think our more episodic approach with response to stimulation going after sort of a signal in the nucleus accumbens that seems to be related to the compulsion to withhold from eating I think is what we will be trying to accomplish uh in our study it's a right now just being conceived though uh yeah these studies they move so slowly because you have to get a grant that Grant gets reviewed by the NIH six months after you submit it often gets rejected because it's too Innovative and too high risk so then you have to edit it and decrease the risk so it takes by obesity so it took two years to get funded and I worry about that time frame because that's a lot of time for patients with anorexia to suffer that I might be able to help at least in a small sample of patients so um but that that is the nature of how these things go you also have to get FDA approval to do these kinds of things we try to do all of this in parallel it's an enormous undertaking and in a lot of ways we're starting from scratch but in some ways we have some preliminary data to go after this so my hope is in about a year we'll have a similar trial for anorexia at Penn so so more to come on that um and and we're not the only lab that's

01:23:14 Non-Invasive Brain Stimulation, Transcranial Magnetic Stimulation

trying to go after because of the the clear need so what is the status of non-invasive brain stimulation ablation and blocking activity in the brain I get a lot of questions about transcranial magnetic stimulation yeah I've actually had that done as a research subject sure when I was at Berkeley Rich Ivory's lab put a coil on my head I was tapping my finger in concert to a uh a drum beat and then all of a sudden uh because of the stimulation it was impossible for me to keep time yes with the drum beat that's cool cool it's a pretty wild experience to not have motor control and uh than to have motor control returned at the flip of a switch when someone else is controlling the switch it makes it especially Eerie um so my understanding is that transcranial magnetic stimulation is being used to treat depression and a number of other brain syndromes non-invasively so no no drilling through the skull the surgeons don't like that surgeons love to cut and drill with purpose but they do um but uh my understanding is that the spatial Precision isn't that great um ultrasound is something I hear a lot about these days um and my

understanding is that ultrasound can allow researchers and clinicians to stimulate specific brain areas perhaps with more Precision um maybe you could just give us a coverage of what those are being used for what are your thoughts on on um uh these forms of non-invasive meaning no no flipping open of a piece of the skull type brain stimulation and blockade of brain activity sure yeah I wanted to clarify also these these surgeries generally don't um by the way require a full craniotomy it's usually just a small opening about the size of a dime in the bone so just just to clarify but that's painless too right uh well usually without pain yeah there's a little bit of scalp numbing we give a scalp block and the patients are getting IV sedations so they in general don't feel anything and if they do they tell me and we give them more local anesthetic but that's they're usually asleep during that part so it's minimally invasive but you know in a lot of ways there's no such thing as a minimally invasive procedure in the brain you know it's a it's kind of so glad to hear you say that oh no I you know I'm I'm not one of those neurosurgeons that you've probably encountered and we have mutual friends that uh and you know these mutual friends are some of my favorite people in neurosurgery and they probably actually think more like me than than not but there are neurosurgeons that you're absolutely right and this is true for all surgeries they really in a lot of ways they think what they do is sort of the ground truth or is it closer to the ground truth and I I get that um uh you know probing with purpose I I actually really like that I'm going to use that if you don't mind um just it's just describing what you do so yeah but I I actually have I've always said this I've said it publicly I've said it to my boss I've said this to my team um we need to embrace non-invasive approaches um some of them are a little fluffy um fluffy in that we don't understand how they work we don't necessarily understand how deep brains too much works by the way so um but because we don't know exactly how they work they're not as precise as we would like them to be so we have work to do there and I actually think that work is doable and actually underway um you know at Stanford we have great collaborators that that I think are doing this people like Nolan Williams and Connor Liston at Cornell and others um so we uh I think that TMS transcranial magnetic stimulation it is FDA approved for depression by the way it's also FDA approved for OCD and for nicotine addiction where do they put the coil for those three or more or less yeah so they put it over was always on the scalp and uh over the frontal lobe and there's different parts of the frontal lobe that have been demonstrated to be a little better or a little bit worse um but what the FDA has approved for depression I believe is uh similar to what's been approved for uh OCD but for addiction I believe it is a

different Target but we'd have to ask our our TMS experts on that can they direct the transcranial magnetic stimulation deep below the cortex they try uh and we're we're actually studying this in OCD patients now um I as a part of our invasive trial uh where we are trying to pull patients from a TMS trial that's in parallel to what we're doing um all funded by the foundation for OCD research where we believe we can use TMs to to define a circuit that if modulated improves OCD albeit temporarily and in those patients if it's temporary they would be appropriate for an invasive study so something we're actively working on I've always believed that neurosurgeons need to be part of the discussion with these non-invasive approaches we don't need to do them but I think we can help make them more precise and to probe non-invasively with purpose rather than this more kind of I don't know a non-invasive blast effect kind of you know I I just can't imagine how that is going to be as effective as probing with purpose but you can do that not invasively as well and I think we need to do better uh in that way I do believe that's possible and I think people are actively trying to do it um getting deep in the brain with TMS I think will always be hard but you can get there indirectly by using connectivity assays and targeting superficial structures that have High connectivity to deep structures so for example um perhaps one day there will be a TMS Target for anorexia and obesity if we are scratching the surface with invasive approaches to these problems we we're even doing less with the brain stimulation um so we have so much work to do there eating disorders and TMS have been so um sort of scarcely studied or or there have been so such little research done in that in that space and so it is an area that we need to to work on um for the obvious reason for example in a patient with anorexia just thinking practically you know placing a device in a patient who is significantly underweight might not be the best approach you know wound erosion and issues like that could come up so developing a non-invasive approach I think is critical the problem is where do we target and so the only way to answer that I think reliably is to accept that we have to get into the Brain before we're out of the brain and with these kinds of conditions we're only just starting to get into the brain you know so I I worry that we're a long way away from a non-invasive approach that really works consistently um sorry to interrupt um I want to make sure we touch on ultrasound because yes um but um his historically it seemed that there was a bit more permission for people to probe around in the human brain I I've um sometimes refer the podcast to some of these papers that were done uh allowing patients to self-stimulate in the brain these are work done in the in the 60s and now his name Escapes Me Robert um anyway there's a couple papers

published in science allowing patients to stimulate a couple different brain areas asking which ones they preferred and I was always shocked and slightly intrigued by the fact that the the brain area that all three of these patients who I don't think had any syndromes I think they volunteered for these experiments I don't think you could do this anymore yes um regulatory yeah yeah I think uh was not the same as it is now things have changed um fortunately but they um all three of them seem to like some midline thalamic structure which for those listening it's just area kind of in the in the dead center of the brain um more or less that evoked a sense of kind of frustration and anger which surprised me because I would have thought oh it's Robert Heath his experiments rather than patients preferring to stimulate areas that evoke laughter or Joy or a feeling of drunkenness or Delight it also explains a lot of what I observe in social media this sort of um kind of people repeatedly engaging in battles um that are kind of trivial it seems like frustration and anger might have its own reward circuitry anyway I don't want to go too far down that rabbit hole but it um it's a deep one it's a deep one and and kind of gets to our nature yeah you know as humans and what we find interesting or rewarding but you know the ability the inability to probe around the brain in a safe way without the need for somebody to be very sick would be I think would be enormously powerful and at least in my mind if I were in charge which I'm not um would offer the opportunity to really come to an understanding about how the human brain works without all these issues of how to translate from Mouse studies and again there's huge value to animal studies as we both agree but um so many of the things that we want to know about the human brain involve asking the person hey do you what do you feel when that set of neurons is stimulated and what don't you feel uh and a mouse we can ask and ask but they're not going to tell us something they do tell us they're not going to tell us in English so um how do we overcome this challenge but

01:32:27 MRI-Guided Focused Ultrasound: Tremor, Essential Tremor & Parkinson's

first ultrasound or if you prefer after ultrasound what is ultrasound going to be really useful towards solving these clinical issues and these basic issues yeah so I think um let's start with ultrasound then we'll come back to it um so ultrasound right now transcranial magnetic magnetic resonance guided Focus ultrasound so um uh this this is an FDA approved method to deliver an ablation to the brain non-invasively there are researchers myself included that are trying to use transcranial magnetic guided magnetic

resonance guided Focus ultrasound or MRI guided Focus ultrasound to use it in a modulatory way not just as an ablation but to drive neuronal activity or inhibit it perhaps we're still learning how to do that um there are trials that are trying to understand if you can use ultrasound to open the blood-brain barrier so you can deliver a medication to that specific area uh perhaps for a brain tumor or something like that so um it's a very exciting field um and it is FDA approved for Tremor right now and so I actually do it routinely um for patients with Tremor with Parkinson's or a central Tremor and so um I I love doing it it's uh often just kind of a miracle because there's no incision I don't have to place an electrode into the brain to achieve a similar result how early into the pathology of Parkinson's can someone think about approaching this so for instance if somebody has a parent or a sibling and they're developing some resting Tremor yeah obviously they should talk to a neurologist but a neurosurgeon but this non-invasive approach could be incredible for them as opposed to just take only taking drugs to increase dopamine levels yeah so um depending on the reason you have Tremor would dictate the kind of medication you would use it could be Parkinson's but if it's not it might be a central Trevor by the way essential tremors 10 times as common as Parkinson's really essential tremor is the most common neurologic condition in patients over the age of 70. we often aren't aware of that people with essential Trevor feel they have their forgotten disease because there's no Michael J fox for a central Tremor I sent a letter sorry is it essential tremor or or essential um I actually sent a letter to Bill Clinton I've observed uh Tremor in him and I think he's actually disclosed that he has it and I hoped he'd become a champion for for patients with a central Tremor um Sandra Day O'Connor does as well she's also public about it but I I was not able to get them eager to become the champion for this condition but like Michael J fox these patients need a champion like that um but unfortunately it's a bit of a forgotten disease nevertheless because of the FDA approval of focus ultrasound for Tremor um another's trying to get some attention for sure and uh it's fabulously effective for these patients it treats patients on one side usually their dominant hand or their worst hand and it um it really speaks to the fact that wow you can deliver non-invasively an ablation to the brain in a hypothesized zone that we think is related to the problem at hand and at least with Tremor it works really well could this be effective for psychiatric disease obesity Eating Disorders uh well um perhaps uh actually that would be the ideal the problem is we don't know where to do the ablation um there is a trial that we would like to do for OCD where we would deliver an ablation to the same area of the brain that we've been delivering ablations to for years

for patients with OCD and it helps a bit that's called a capsulotomy um but really the outcome is probably going to be about the same it's a nice method because it's non-invasive but we need to find a new Target for these for these conditions and because of the common denominator of the urge despite the risk sort of that compulsion um yeah perhaps it could be the same Target I don't know um but I would argue we need to do these modulatory experiments either with a device or with uh invasive recordings uh to better understand where these

01:36:40 Future of Non-Invasive Brain Stimulation, Epilepsy & Depression

problems are coming from to Define where we should do an ultrasound treatment so um you're right historically without much regulation we've we've probed the brain um the problem we can't learn a lot from those experiments now uh well in this way at least we don't know exactly where those electrodes were we didn't have MRI scanning or high quality cat scanning to to know where those electrodes were with certainty where and we know two or three millimeters matters and we also didn't have the tools to place electrodes in a precise way back then so unfortunately we can't learn a lot from those experiments right now so we're sort of redesigning them and there is a way to do it now um patients with epilepsy benefit from this all the time there has been a revolution in America it was in Europe before it was in America where we would do stereo encephalography which is basically like doing an EEG of patients with epilepsy but with invasive electrodes and we would Place tiny little wires less than a millimeter in diameter all throughout the brain into parts of the brain that we believe are involved in seizures and we would admit the patients to the hospital and figure out where the seizures were starting and propagating and then um you know we could stimulate these electrodes to see if there was a symptom that was important and I try to identify a region that we thought we could either remove surgically ablate with a laser or put a stimulator in it perhaps that's commonplace now for epilepsy um and it works extremely well and it's very safe of course it's still a brain procedure but the uh the complication rate is surprisingly low quite honestly for the amount of electors that we place um and it's extremely well tolerated most these patients leave the hospital and they don't even feel like they've had surgery so uh there's actually a lot of interest in using that procedure to study mental health disorders we are trying to do it for patients with obsessive compulsive disorder we're awaiting an FDA decision on that uh but actually I credit uh

our colleagues at Baylor and at UCSF for for studying this uh already we have fabulous colleagues at UCSF that have studied depression using this type of approach a mutual friend of ours uh you know Eddie Chang who's a wonderful friend and colleague somebody I've emulated for many years as well uh and and the the Psychiatry team at UCSF have worked together on this sort of bringing together the epilepsy technique and the Psychiatry expertise to study how we could better Target electrodes in depression and I'll tell you if they have a consistent Target perhaps there becomes an ultrasound Target um but right now the approach is a bit more reversible because you can always shut that electrode off or even remove the electrode if perhaps it's not in the optimal location to treat the depression uh but actually after a large volume of cases perhaps they could pool that data to develop a a new ultrasound Target for depression I think that would be fabulous and probably is their long-term goal um not to speak for them but that would be something that I I'm sure is on their radar and a Baylor is trying to do the same thing for depression their approaches are a little bit different but a similar tool to try to understand uh depression and you know we're working with all these types of uh colleagues some of these are our friends to try to to bring this to OCD as well and you know it makes sense to try to do this for addiction and obesity and anorexia you might ask well why aren't you doing this for obesity right now in uh in our in our study and the reason is that um we've developed a target for obesity uh and binge eating disorder uh developed out of mice that we believe um is relevant for the human State because you can model this problem in a mouse a bit better than you can model depression or OCD so we feel like we can rely on the pre-clinical studies more whereas with these perhaps more I don't want to say more complicated but more human mental health conditions that are hard to model in a mouse you really have to study it in the human and you can perhaps start in an epileptic patient a patient that has electrodes and try to provoke a depressed state or study epileptics like Dr Chang has done that have comorbid depression for example and that can really validate this approach as well but in the end it's it's getting into the human brain that we need to do in the disease specifically that will eventually lead to a non invasive approach either a lesion or modulatory approach modulatory would be like TMS or lesion approach would be with ultrasound couldn't agree more meanwhile because there are many many millions of people suffering from depression Eating Disorders Parkinson's and essential tremor Etc well first of all I should say based on everything you've told me thus far it's amazing to me that any pharmacologic treatments work because of how systemic they are and impacting

serotonin serotonergic neurons over here in dopaminergic neurons over there and not targeting any specific batch of cells it

01:41:51 Pre-Behavioral States in Compulsion & Awareness, Mood Provocation

makes perfect sense as to why all the side effects exist but earlier you said something that really grabbed my attention I want to come back to which is that if people can be made to feel or make themselves feel just a little bit better a little less anxious just prior to a craving episode or a binge episode maybe even if people can become better at detecting their own internal States and when they're kind of veering toward a binge or veering toward using a drug or maybe even veering towards suicidal thinking I based on what you said earlier that those kind of um pre-behavioral States the kind of drift on the on the steering um those sound like powerful levels of awareness at least for now until we have specific sites in the brain that we can Target non-invasive methods that could be deployed to millions and millions of people seems like that awareness seems like maybe among the best tools that people could develop yes 100 agree with you you know so for the person with OCD or uh who suffers from anorexia or binge eating disorder and to their clinicians you know I I just want to highlight that you said that I mean I'm not again I'm not a clinician I always say this I don't prescribe anything I profess things um and uh but awareness of one's thinking seems immensely powerful in this context yeah um and after all it is the clinical probe that you use because the if let's say the patient were to lie to you about their experience of what happens in their mind when you stimulate you could basically the whole thing the whole surgery the whole procedure could go badly wrong so it's it's up to the patient to be of course honest with you in their their incentivized to do that but to be honest with themselves about ah you know I've gone all day without a binge but you know the the smell of a donut or the thought of a donut is starting to have a particular Allure that awareness seems like an incredibly powerful thing to own and to and to build and cultivate yes I've always thought that if we could improve awareness we can improve outcomes I think that's probably true for many of these patients the problem I think comes down to the fact that some of these patients are so resistant to treatment and the patients that we see as a surgeon for example are the patients that they've tried cognitive behavioral therapy certainly have tried medications they've tried Behavioral Management they are aware of their problem and they've shown that to us they can tell us when they're craving but despite the

craving and despite being involved in this invasive brain surgical trial highly you know first in human novel study which I think will have a positive effect but it's still experimental uh they still can't stop themselves so there sort of as made aware as could possibly be did I use grammar there correctly I think so um they're as aware as they could possibly be and they still lose control we've had this studied in the lab so we will bring patients to the laboratory with this implanted device to to try to provoke this electrographic electrical signal that can be detected by the actual device that will stimulate them when they're at home but before we actually initiate stimulation we want us to see can this device detect this craving cell signal which is going to be different than what we saw in the operating room because that's a single cell but these devices these electrodes are about a millimeter in diameter instead of like a tenth of a millimeter which is what we use in the operating room um so they're they're only hearing or or detecting I should say thousands of cells responses and we actually have a way to provoke binges it's called a mood provocation it's very well well very well validated it's a little bit like provoking seizures in the epilepsy monitoring unit but here in these sort of uh psychiatric monitoring unit or the the food monitoring unit uh we we actually have a psychiatrist and eating disorder Specialists come and induce a mood that is related to each patient's sort of self-described binge episode so the psychiatrist comes in and provokes yes a feeling that can evoke the negative behavior that's exactly right so that we can video and synchronize the video to the brain signal recordings um the patients all wear an eye tracker so we can see what they're eating at all times and what they're looking at specifically and that allows us to have the best temporal resolution possible to understand what is happening right before the bite and even under video surveillance through a one day one-way mirror in a laboratory setting when patients are very well aware that their there to be studied if they're going to binge they still do and we believe they do because they just can't control it as aware as they are of it and it's probably because they're the most severe so I think if we can improve awareness not just the societal awareness that I was talking about earlier but the patient awareness around their problem I think that could be a powerful way to help so many of these patients and that's sort of the role of cognitive behavioral therapy um the problem with cognitive behavioral therapy or should say the limitation of it I actually don't have any problem with it I think it's a wonderful treatment um is that if you stop it many of these patients go back to their old behaviors I don't say old habits but it might be a habit but the old behaviors and so um that's the problem is it's not necessarily lasting in the absence of continued

cognitive behavioral therapy some people can benefit from it long term but some can't uh but I think in in in the less severe patients improving awareness key but in these really refractory patients this is this is kind of like this is the disease despite the awareness they can't control themselves and that's what we're trying

01:48:02 Machine Learning/Artificial Intelligence & Compulsion Predictions

to restore is that improved ability to control their behavior do you think there's a role for machines and artificial intelligence here uh there are a couple Laboratories up at the University of Washington that are using particular signature patterns of within voice to try and help suicidal people who are suicidally depressed know when they're headed towards an episode before they even can consciously know so this gets right down issues of Free Will and whether or not machines can be smarter than we are but you know one could argue that some of the search algorithms on Google and other search engines are actually more aware of our preferences than we are um basically what these are these are devices that are listening to people talk all day they're also paying attention to patterns of breathing and how well people slept Etc integrating a huge number of cues and then signaling somebody with a you know a yellow light like you know you're headed into a depressive episode the person might say I feel fine or I feel pretty good this is kind of Baseline state for me and they say ah this is where you were preceding the last episode that took you down a deep dark trench and it took months to get out of um I wonder whether or not some of these devices could help with the sorts of things that we're talking about today yeah I think so um I've always said we have to get in the Brain before we get out of it and if we get in the brain and understand what these signals look like we'll know what those non-invasive signals are I think it's possible that we are scientifically sophisticated enough to use machine learning um and sort of this kind of botan technique to anticipate when somebody is going to be highly impulsive you know suicide it's the most dangerous impulse it's something that is immensely a focus of the lab is impulsivity we've talked mostly about compulsion compulsion being you know going after a reward or the urge despite the risk um impulsivity is is similar but different it's it's kind of going after something um a little bit if you if you model impulsivity in a mouse it's you know related to you know going after a food reward without the sort of paired tone that your the mouse is supposed to wait for the mouse doesn't want to wait anymore they just go after the food um I've been that Mouse yeah we've all been oh we

could all relate with this uh to a certain extent against the Spectrum so um so in any case I uh non-sequitur but I I I certainly think that there is a way to use our own body's physiology to anticipate when these impulses are coming online how best to do that I think we're just scratching the surface but these are the kinds of solutions we need these are some of these problems are of epidemic proportions the largest public health problems in this country in this world obesity opiate crisis depression suicidality I mean that's like a third of our country maybe more probably more and think about it and a colleague of ours at Stanford Psychiatry told me something that still just blows my mind which is that something like 75 percent of the antidepressant and anti-anxiety medication that exists in the world is consumed in the United States it's amazing which is I mean that's an outrageous number yeah we do have an obsession in this country for pharmacy you know and the pharmaceutical industry is very powerful here and probably related some aspect of capitalism I'm capitalistic and just like everybody else but um I do worry about that a little bit um but you know we tend to over prescribe and I think we as patients tend to over want medication we like quick Solutions and sometimes medications provided sometimes not or they're often just abandoned depends on the problem of course so um but but I I agree that we need scalable Solutions but you know I'm a neurosurgeon I'm only going to be able to treat the most severe of patients with these problems you know you know we've only done about 200 000 deep brain stimulation surgeries ever so I mean the problem we're talking about here is 50 million Americans there's no possibility that surgeons can address that problem but we could help Inspire an initiative to go after that kind of problem or help make it more rigorous because the last thing we need is a you know some sort of wearable fancy tool that you know uh waste people's money and time you know we need real therapies for these things not that these devices that we're discussing are not uh I think actually there's lots of promise we use machine learning in the lab all the time I'm not a an electrical engineer or the computational neuroscientist doing this type of work I I just helped develop the hypotheses around it but um and help fundraise around it but I I definitely think there's a future for it I just I I

01:53:05 Neurosurgeon Hands, Resistance Training & Deadlifts

suspect we're scratching the surface on how best to do it let's talk about your hands yeah sure all the neurosurgeons I know are you know very Faithfully protect their hands

because talking about insurance is too expensive that's it right but I'm guessing that you you all are not the ones to reach into the garbage disposal even if your eye is on the switch to make sure that it isn't going to get turned on they're just too precious they are your livelihood yeah um and earlier we talked about deadlifts uh there are other forms of exercise um they're things like tennis um they're they're drawing and painting a full range of things that one can do with their hands use your imagination sure um is it true that neurosurgeons don't do any uh really like heavy grip activity because it can refine the motor motor circuits in the brain and elsewhere that can throw off their neurosurgery game I would say that many neurosurgeons uh avoid activities that put their hands at risk um another one by the way you know there's a uh an annual uh softball tournament uh that uh neurosurgeons come to in New York City in Central Park with a very softball no I'm just kidding well actually it's actually a very you know typical hard softball I don't know why they call it softball and uh actually a two close colleagues of mine have gotten injured at that tournament maybe this is a it's also I must say and here I'm poking fun but for those of you who are going in the medical profession it's also one of the more uh how should I say this well I'm just going to say it there's a steep hierarchy of training in neurosurgery yes um there's a certain harshness that's been conveyed to me about the training uh much like Astronaut training to be totally fair and so maybe this is a tactic to uh to weed out either the younger or the older generation it says Evolution right we uh have to evolve and we need in medical the week I guess well I I could say that one of the individuals that got injured is one of the more senior surgeons that I work with now and is one of the best athletes that I know and he's definitely not weak but you can get injured playing these Sports and uh that being said I can tell you briefly is um I think that you know it's funny my my mother came to me recently she's she has osteopenia and she told me her doctor told her she's not allowed to do deadlifts and I was like okay um that's fine uh I'm not telling you you should do deadlifts I just don't exactly understand the relationship but um I can say that I do think I'll give you a little story here the reason why I'm being a little hesitant to to confirm that I agree with you on the deadlifts is I um when I was operating this is when I was at Stanford University operating and uh we as I mentioned earlier we get an interoperative CAT scan uh to confirm accuracy of our lectures I do this for all of my surgeries when I was reviewing that CAT scan the x-ray technician looked at me and said whispered into my ear he's like your posture really bad embarrassing your physical posture while doing your surgeries yeah and I looked at him and I kind of wanted to say I won't curse but yeah exactly I've been doing it intermittently

during our conversation because he made me realize that I really did have bad posture and um we kind of had a little brief aside and he I learned he was a personal trainer and uh his name was Zach and he uh you know he said to me you know your posture is weak because or your posture is poor because you're weak you need to strengthen your body and strengthen your core I was like how he's like power lifting and I'm like I'm a little hesitant to do this and I'll tell you I started very slowly and I can't prescribe power lifting to everybody for the exact reason you said um and I've gotten hurt doing it by the way but I do think I I wish I started a little younger and I would argue that with close supervision and very well if you are if you have a very experienced trainer which I would argue if you're a neurosurgeon or an astronaut uh or or have a highly specialized profession where you need your your limbs to to function dentists things like that um if you're going to take something on like this it really needs to be extremely carefully supervised and I can tell you that you know my trainer had a profound impact on my life and my posture and my my physical health and so uh we did deadlift I'll admit so when you brought it up I kind of chuckled to myself but uh yes I I have gotten mildly hurt deadlifting but it was when I was doing it by myself and I was kind of cocky and I wasn't paying attention but when I was with him and he was all over my technique it actually was the most efficient way for me to feel stronger and it improved my posture uh significantly and I I miss him since I left California I I have a new trainer in Philadelphia who's great but uh uh and and I still deadlift occasionally with him but I uh I I can say I I am opposed to deadlifting callously but if you're extremely well monitored by it experienced um personal trainer or weight lifter uh I think it could be a great exercise great I love to be wrong in this case um because I'm a huge proponent and on the podcast I go on and on I mean they're so there's so much data now pointing the fact that 100 and 180 to 200 minutes of Zone 2 cardio kind of jogging cycling swimming type behavior is very healthy for everybody and we should all be doing that at least that yes I need to as well and that resistance training on the order of you know six hard sets per muscle group per week are it's really important just to offset deterioration of muscles and I'm learning skeletal function and tendon strength and that's just to maintain we're not talking about all out sets to Absolute failure but as you point out with um with proper form so even the

01:59:00 "Neurosurgeon Calm," Quality Time & Prioritization, Neurosurgeon Training

neurosurgeons are doing this which I think is is wonderful yes as a final question um but one that I think really or maybe second to final question earlier I commented on the remarkable calm at least perceived calm of neurosurgeons it could be caused or could be effective the training but it's obvious to me why one would want that trait in their neurosurgeon um I wouldn't want to hyperactive certainly not an impulsive neurosurgeon given that the margins of error are so so tiny the spatial scale and probably on the temporal scale too yes and you don't want people doing things in time that are or being spontaneous at all do you think that this branch of medicine that you're in selects for people that at least can know how to control any kind of fluctuations in autonomic growth so they can calm themselves in real time and here's a specific question when I've never operated on the human brain although I've had the privilege of being in the operating room and seeing this with some of our experiments with people in VR it's a remarkable thing I wish for everybody that would get this experience at some point not hopefully as a patient unless they have a need but to observe it but what was just striking to me is the various uh stereotype behaviors of the surgeon and when I did surgeries as a graduate student as a postdoc in the brains of other types of animals I would find for instance that if I started to tremble a little bit if I tapped my left foot that my hand would stabilize a bit that there's this kind of need to move the body or one feels the impulse maybe that's my my Tourette's like compulsions again but but that one can kind of um siphon off some of that energy into another limb so that you could remain precise so are these sorts of things that I'm talking about are maybe it's entirely my imagination but are these the sorts of things that one learns as a neurosurgeon how to still the body and still the Mind do you have a meditative practice when you go into the operating room if you had a particularly challenging morning or or a poor night's sleep do you have tools that you use to calibrate yourself and get yourself into the Zone I think this would be very interesting for people to get some insight into even if they don't want to be a neurosurgeon yeah I completely agree and I I appreciate the earlier uh reference to neurosurgeons as uh astronauts because I've also heard you know us compared to Cowboys before and it's a little bit less flattering I uh you know some of what we do surgically really does require a substantial amount of confidence um and that confidence hopefully comes from years of training and experience um you always worry that the confidence is sort of misplaced and that that is problematic luckily I you so rarely see that because our training is so rigorous you know we have a board of uh American Board of neurological surgeons that uh sort of allows and and assesses surgeons to continue practice and holds us to a

really high bar I do think it tends to attract a certain personality uh in my sub-specialty as a like a deep brain stimulation surgeon we call it stereotactic and functional neurosurgery you know some people have likened us to the neurologists with a scalpel um we we tend to be a bit more intellectual um uh maybe maybe bedside manner is a little bit friendlier um and then there's the vascular neurosurgeon who doesn't sleep and so they're not as friendly there's the spine surgeons who operate the most and so they're you know busy busy busy uh we there are some of these kind of reputations going around but I I agree with you there's a sort of a common feature of of a calmness across neurosurgeons and you know there's some of my obviously my favorite people my closest friends um and I I can relate with them probably because of that um sort of a big picture they don't get sort of uh flustered uh they they tend to are they tend to be really good at figuring out how to have quality time because we work really hard our hours are uh significant and so the time with our families our friends is less than we would like it to be um that obviously that's true for people who work hard across any profession but definitely true for neurosurgeons and I think that we're very good at figuring out how to make that time high quality um you know even just texting with some of my friends um in that are that are neurosurgeons a great friend of mine just became chairman at Duke and just connecting with him by text which takes seconds you know you feel we feel connected you know and I I think that's a that's a trait amongst neurosurgeons we sort of know how to cut to the chase in a way um and prioritize our time it's a skill that we probably have innately but is also part of the training you know when we are interns now there's a lot of work hour regulations that is probably quite appropriate by the way um I I think our hours before were bordering uh on on uh on not necessarily let's just say they were not ideal for mental health and sleep which we know are very important components um certainly we had no time for meditation I definitely did not I wish I did um now knowing what I know about meditation my wife's a health coach I I get it I see it I I practice it myself with her um I see the value I wish I had that tool when I was in training because it's stressful um you know you even with workout restrictions we still don't sleep very much we're still at work a lot about 80 hours you know a week throughout the entire career uh there are times when it's more because after training there's no work hour restrictions so sometimes I feel like as faculty we get abused and the trainees are a little bit more protected now it definitely was the reverse at one point and that's also a huge problem probably more of a problem um and I'm joking a little bit I don't necessarily think we're abused but certainly our hours are significant um but you know they come a bit

more here and there you know on my or days when I'm operating those are long days but on the days that I'm lucky enough to be a researcher you know uh like you those days tend to be a bit gentler unless I'm great writing those days can be long as you know um so I so to answer your question I do think we're we're sort of self-selected for it but I also think it's part of the training you know we because of the long hours that we're in the hospital we're taking care of sick patients and we have sort of a type a mentor approach where our mentors are hard on us you know we learn to cope with our stress and be efficient and prioritize things despite the stress of it all and I think you know we take from that this sort of calm demeanor and you know perhaps um perhaps it's just amplifies what we were probably drawn to because before we come to neurosurgery we want rotated neurosurgery we might spend a month you know pretending to be a neurosurgeon learning from residents and and faculty that are practicing the specialty but you know prior to actually starting your training you you never experience anything like being a resident in neurosurgery uh the stress and the volume of patients that you have to take care of and the long nights it can be quite Lonely by the way um you develop friends in the hospital but sometimes you're on your own when you're on call and you have backup you can call your chief resident or you're attending but you really have to learn how to take care of patients yourself you obviously form teams with nurses and staff and things like that and other residents but it can be lonely it can be really challenging and I think because of those experiences that all neurosurgeons go through uh you know we tend to have this sort of unflappable personality that perhaps we started with a bit compared to the average person but the training definitely amplifies it and do you have tools that you implement if you ever feel that you're getting slightly off-center I do now um you know I when I was in training I actually remember in my second year so most neurosurgery programs when you're a junior resident in some ways that's your toughest year not in every way um it is your toughest year because you're you're young and you're inexperienced and you don't know what you don't know and and that that's why it's such a tough year because you have to learn a lot very quickly for patient safety reasons for self-survival you know you just have to learn a lot um and you're on call by yourself in the hospital and it's uh it's a real Challenge and I think that you know I you know personally I I gained a lot of weight during that year the only exercise I did consciously was taking the stairs I refused to take the elevator and I was at uh Penn at HUB where I currently practice now and I remember I would see patients anywhere from sort of the ground floor where the Chama Bay was or the ER all the way up to Founders

12th 12th floor and I would never take an elevator that was my rule for the year because I knew I would not have time to exercise but I would just take the stairs and in the beginning of the year I would be a little winded when I got to the 12th floor but by the end of the year actually it didn't really phase me it became a great habit to have um the problem with that though is I paired that unfortunately with you know a lot of sleepless nights or not enough sleep let's say and I had this terrible habit of drinking coffee late at night and I would put a lot of sugar in it and it was sort of the only way for me to get a quick you know um a quick bout of energy that for some reason I prioritized at that time obviously knowing that I would crash which I always did and I always kind of regretted it but I still did it anyway and I attribute that to poor decision making inexperience um and perhaps being a little vulnerable like I think we all are that's why I relate with a lot of the research that I do and I remember I got married in my third year the year after my second year and my wife and I or my fiance at the time we started going to the gym together in the morning and my hours were a little better so I would actually be able to exercise before I operated that day and I operated almost every day as a third year resident so I remember I'd get to the gym really early in three months I lost like 20 pounds and I wasn't trying to lose weight I just was sleeping better and taking care of myself and I remember when we got married I fit into a tuxedo that I had in college or it would have fit me in college it actually was a new tuxedo admittedly but it was the same size as my tuxedo from college so I think that um I've always related with the problems that our patients have to a certain extent and you know I when I've been most vulnerable which is what I was working the hardest with the least

02:09:53 Daily Habits: Sleep, Exercise, Meditation

amount of sleep I related with it the most and yes exercise for me has always been my tool um more recently exercise some some you know strength training I think is important compared with cardio um I don't do enough of either um but I definitely do some and that helps meditation helps me a bit we I do that every night before I go to sleep um you know I use an app for it it's probably not the best way to do meditation but if it keeps you doing it regularly that's the best way to do it Andrew I couldn't agree with you more you know it's one of those things where I look forward to it every night and you know sometimes my wife falls asleep and I come to bed a little later and I whisper I'm like are you okay if I turn the app on so you know she does the same to me because

I think we both value it and I think that's that that's been very helpful I didn't have that tool probably what I needed it most but I have it now and it's very helpful I really appreciate you sharing those tools a number of people uh I'm guessing out there might want to become neurosurgeons I really believe that in hearing today's conversation that you will spark an interest in medicine and or neurosurgery um well certainly you need to be a physician before you can become a neurosurgeon so end neurosurgery in some cases and that would be beautiful and I predict that will be happen that will happen excuse me as a consequence of um what you've shared today I really appreciate your mentioning of the um emphasis and appreciation on quality time uh I very much see this as quality time I know that our listeners were will as well really want to thank you for taking time out of your not just immensely busy but very important schedule because again the work that you're doing is really out there on that cutting I don't want to say bleeding edge because in this context it's not going to sound right but on that extreme Cutting Edge of what we understand about how the human brain works and how it can be repaired um they're doing marvelous work will Point people to various places they can find you online and should they need your the help of your clinic to to your clinic and your laboratory as well so on behalf of everybody and and myself as

02:11:59 Zero-Cost Support, YouTube Feedback, Spotify & Apple Reviews, Sponsors, Momentous Supplements, Neural Network Newsletter, Instagram, Twitter, Facebook, LinkedIn

well thank you so so very much I'm honored thank you so much for having me thank you for joining me today for my discussion with Dr Casey Halpern about the use of deep brain stimulation and novel Technologies for the treatment of eating disorders and movement disorders of various kinds for those of you that are interested in learning more about Dr halpern's research please see the links in our show note captions that include links to his laboratory website and to his Clinic as well as various research Publications that are available in complete form as downloadable PDFs if you're learning from and or enjoying this podcast please subscribe to our YouTube channel that's a terrific zero cost way to support us in addition please subscribe to the podcast on both Spotify and apple and on both Spotify and apple you can leave us up to a five star review if you have questions for us or comments or feedback of any kind please put that in the comment section on YouTube we do read all the comments please also check out the sponsors

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