Project Sleep Narcolepsy Nerd Alert
The Science of Narcolepsy (Season 1, Episode 9)
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In today's episode, Julie and Dr. Scammell talk about some of the science behind narcolepsy including talking about hypocretin or orexin levels, whether cataplexy can develop at a later stage, potential preceding factors to developing narcolepsy, and theories on how narcolepsy develops in the brain.

The Narcolepsy Nerd Alert series invites listeners to dive deeper into specific topics relevant to living with Narcolepsy. This is a written transcription of the podcast "The Science of Narcolepsy" (Season 1, Episode 9) from Project Sleep.

Project Sleep is a 501(c)3 Nonprofit Organization, dedicated to raising awareness and advocating for sleep health, sleep equity and sleep disorders.

All guests and speakers express their own opinions. While medical diagnoses and treatment options are discussed for educational purposes, this information should not be taken as medical advice. Each person's experience is so unique, which is why it's so important to always consult your own medical team when making decisions about your own health.

Julie in intro: Today I am joined by a renowned narcolepsy expert, Dr. Thomas Scammell, to answer all your questions about the science of narcolepsy. Like, what causes narcolepsy? Is it genetic, or are there environmental factors? What are orexins, or hypocretin? And how do losing these neurotransmitters impair the wake promoting systems? Dr. Thomas Scammell is a professor of neurology at Harvard Medical School, Beth Israel Deaconness Medical Center, and Boston Children's Hospital. He has published over 150 journal articles and chapters, and lectured around the world on narcolepsy and the neurobiology of sleep and wakefulness.

Julie: Hello everybody! We're so excited for todays topic, science of narcolepsy.

Dr. Scammell: Just to kind of wind back— like, way back— narcolepsy was first described by doctors, you know, of course it's been around forever— but it was first described by doctors in the 1870's. And it was honestly, completely, profoundly mysterious until about 20 years ago, when it was found that narcolepsy type 1 is caused by a loss of the neurons in the brain that make orexin which is also known as hypocretin. So on the clinical side many of you might have heard of that— you know measuring hypocretin levels. I think the term orexin, which means the same thing, is going to become more and more prevalent as drugs that target this become used more frequently. This incredible discovery, it's from Emmanuel Mignot, where he's

compiling the results of a few different studies, so in the control people— the levels of orexin ranged from a little more than 200 up to around 600 and the average level's around 320 or so. But in people who have narcolepsy with cataplexy, thats type 1 narcolepsy— 90% of the time their levels are super low— meaning less than 110 picograms per mil on the scale. Very few people who have honest to goodness narcolepsy with cataplexy have normal-ish levels of orexin and so that's— that's huge. Type 1 narcolepsy is caused by orexin deficiency. People who have narcolepsy without cataplexy, thats type 2 narcolepsy, usually have normal levels. It's a similar appearing disease, but it has a different cause and we actually still don't really understand what causes that. So this loss of orexin in spinal fluid is due to a loss of the orexin producing neurons.

Dr. Scammell: In The International Classification of Sleep Disorders, which is what most doctors use to diagnose this, we now recognize these two types of narcolepsy— narcolepsy type 1, which used to be known as narcolepsy with cataplexy and sometimes this is abbreviated as NT1— and to make this diagnosis, you need to have chronic sleepiness, of course. And then you need to have cataplexy— plus a multiple sleep latency test that's considered "positive" meaning you fall asleep quickly, less than 8 minutes, and you have REM sleep in at least two of those naps that occur on the multiple sleep latency test.

Dr. Scammell: Another way to get that diagnosis is to have a spinal tap and to measure the cerebrospinal fluid orexin concentration, and if its super low— then, that also provides really strong evidence for narcolepsy type 1. Narcolepsy type 2 is diagnosed by the presence of chronic sleepiness plus this positive MSLT. And I have to say, in my clinic a lot of the times when somebody sort of meets those criteria, I'm not 100% confident that that's really what they've got, you know, whether it's narcolepsy type 2 or this kind of related disorder called idiopathic hypersomnia. 'Cause a lot of this hinges upon the results of the multiple sleep latency test, and sometimes people have— two naps with REM sleep, sometimes they have one. And that can actually really impact whether you're diagnosed as idiopathic hypersomnia or narcolepsy type 2. I think many people who are listening in probably also recognize that in narcolepsy there's more than just sleepiness and cataplexy— people can have hallucinations around the edge of sleep, these are called hypnogogic hallucinations. They can have sleep paralysis, where when you wake up you can't move— and they can of course have fragmented sleep which is lots of spontaneous awakenings across the night. And these are all generally more frequent and prevalent in type 1 narcolepsy but they're still found in type 2. But they're also kind of found in the general population so diagnostically they're not super helpful for doctors— but of course they're important symptoms that we sometimes need to target.

Dr. Scammell: Sometimes people with narcolepsy, particularly type 1, will go into REM sleep super fast at night. Normally, it takes 60-90 minutes to get into your first episode of rapid eye movement sleep, but especially in type 1 narcolepsy, people can get into REM sleep in— less than five minutes. And if it happens in less than 15 minutes that's actually included in the tally of those REM episodes that can help support the diagnosis.

Julie: Dr. Scammell was my doctor— [laughing] and diagnosed me with type 1 narcolepsy— 14 years ago. And I remember you saying that I went into REM sleep so quickly in all 5 of my naps. It seems to be very defining, that test— the MSLT, for type 1— and I don't know if we want to talk about it now, but I mean something that— that's hugely curiosity for me is, this type 2 narcolepsy versus idiopathic hypersomnia diagnosis. And I imagine like you said, like many people that are tuned in, they often like sometimes even get their diagnosis changed— if they go to a different doctor, or have a second sleep study, and— um, I was just kind of wondering, do you think this will evolve? The titles of these?

Dr. Scammell: Well, I think we can do better. So I think in general it's— for a doctor who knows what they're doing— diagnosing narcolepsy type 1 is usually pretty straight forward. Cataplexy is very, very distinctive usually. And as you say, many times on the multiple sleep latency test, people have strikingly positive results. You know, REM sleep like you say, in many of the naps. And it actually— you know even though you only need REM sleep in two of the naps to meet criteria, most people wth type 1 narcolepsy will have it in 3, 4, 5 of the naps like you did. And they have very short REM latencies.

Dr. Scammell: But type 2— type 2 is hard— because, just I completely agree with you. The term that we use for this is, test re-test reproducibility. Right? And so, if you do the multiple sleep latency test today and then you do it again in 6 months, are you going to get the same results. And little tiny variations in normal biology and environmental things can make a difference. Like maybe somebody just falls asleep a little shorter, maybe the room's hot. Maybe there's noise in the hallway. Maybe they didn't sleep well the night before, you know there's all these things that can impact this, and so— the truth is, you know, several research groups have now found that in type 2 narcolepsy the results of the multiple sleep latency test are kind of fickle. And so, I think we trust it less than we used to. When these definitions were made about ten years ago, people were like, oh this is great. We've got these nice tidy diagnoses. But now, I think we sort of recognize, it's like— ehhh, that diagnosis of type 2, it's something that should have a question mark after it much of the time. And unfortunately we don't have a better way of diagnosing it yet. There's a lot of interest in this, of looking at other— physiologic biomarkers. Okay, are there things in the brainwaves, or the sleep patterns, or other things you can measure in the blood— that may be helpful for teasing apart type 2 narcolepsy and idiopathic hypersomnia. And thus far I would say, theres not too much thats super distinctive.

Dr. Scammell: There is some aspects of, nighttime sleep architecture— the different stages of sleep, that might be somewhat useful. Like idiopathic hypersomnia patients tend to have less fragmented sleep, they tend to have longer more monotonous, non-REM sleep stage N2— but this is, it's all kind of, preliminary and I don't think theres anything you can really bank on yet thats going to be diagnostically definitive.

Dr. Scammell: So, on the plus side— We treat all these with the same medications. And one would hope that, in general with enough perseverance from the treating doctors, it should be possible to get the right medicines to the right people. But there are some insurers who— who say well we don't really have any approved medicines for idiopathic hypersomnia— [laughs] and in that case, it would be a lot more convenient to have a narcolepsy diagnosis.

Dr. Scammell: 20 years ago researchers discovered that narcolepsy's caused by a selective loss of the orexin or hypocretin producing neurons in the brain. Now what caused that— wasn't clear. It was known since the 1980s, that narcolepsy is strongly linked to a particular genetic marker— it goes by this awkward name of HLA-DQB1*0602. It's a gene that shows up in lots of people with type 1 narcolepsy and many people with type 2. Specifically, over 90% of people with type 1 narcolepsy carry that gene. We call it 0602. And over 50% of people with type 2 carry that. The gene however is found in the general population and, depending on which country, you know— 10-25% or so. And so, just having the gene alone doesn't make you develop narcolepsy. But it does seem to be a fairly necessary pre-requisite for developing it. Very few people who have type 1 narcolepsy lack 0602. So it kind of sets a genetic foundation, and if you've got that, you could develop narcolepsy at some point during your life.

Dr. Scammell: About 10+ years ago, something horrible happened. In northern Europe. Around the world there was this flu going around that was called the H1N1 flu, and it was pretty bad flu, and it was a lot of people dying from it and governments around the world were really eager to get their populations vaccinated. And so they made a big push, and different brands of

vaccines were developed in different countries. And in northern Europe there was a vaccine that went by the brand name of Pandemrix— that was used. And it was a very effective vaccine, it stirred up a very strong immune response against this H1N1 flu. But a couple of months after it was given, doctors started seeing lots of kids and young adults developing narcolepsy.

Dr. Scammell: And in 2002, 2003, 2004— there's hardly even one— there's less than one kid per 100,000 kids— um, developing narcolepsy per year. But then in the winter of 2009-2010, when this vaccine was used— that number shot up to over three and a half kids per 100,000. In the 11-16 year old group in red, there was an even more obvious spike where they went from about one kid per 100,000 getting narcolepsy— to now it was eight or nine. And you can see the same thing is true for 17-19 year olds, and it's not so obvious for the older people— the over 20 years old. That there wasn't such an obvious spike, and— subsequent research it does look like young adults might've also had a small increase— in new cases of narcolepsy after receiving this vaccination.

Dr. Scammell: Subsequent research showed that the number of cases went back down to it's background levels in the subsequent years. And so— overall, what happened was— that if you got this vaccine, this particular brand of vaccine— it produced about an 8-12 fold increase in new cases of narcolepsy, but it was mainly in children. And these— these vaccines had, something mixed into it called an adjuvant, that stirs up a strong immune response and in this case it was ASO3— which isn't used in vaccines anymore after this happened. And so, all these kids who got narcolepsy after given this vaccine, turned out to be genetically vulnerable — they all carried this 0602 gene— and for the most part they developed narcolepsy, NT1 that is— type 1— about 40 days after getting the vaccine. And so what this shows is something super important, I mean— the whole thing is terribly tragic, but it teaches us a lot about narcolepsy. It shows that, first— you need to have this gene— to develop narcolepsy. The 0602. Second, certain age groups are more vulnerable to develop narcolepsy. And in this case it's children and teenagers, and— that's when narcolepsy generally develops anyway. And then third, there's got to be some kind of immune stimulus that's— that kicks the immune system in a way that can cause it to attack those orexin or hypocretin neurons in the brain.

Dr. Scammell: And so, in the subsequent years, Dr. Mignot, some groups in Europe— have— oh, Dr. Basetti, collaboratives in Switzerland— found specific immune cells that target the orexin or hypocretin neurons. And some of these immune cells cross react with some of the things in this particular Pandemrix vaccine. So what we think is going on is that— when kids received this vaccine, their immune system responded properly— it made immune cells that were targeting the proteins in the vaccine, and that's good— 'cause that's prepping it to fight the flu if they ever encountered it. But some of those molecules were probably rather similar to molecules found on the orexin neurons and so those immune cells cross-reacted with the orexin neurons and killed them, as well. And so, it's this case of what we call molecular mimicry — where the immune system is getting confused and its— it says, oh I'm attacking the flu. But it's actually attacking the orexin neurons, as well.

Dr. Scammell: It's like a perfect storm. You're born with certain genes, you got to be a certain age, and there's got to be something that stirs up the immune system in a bad way. And now, one thing that I want to emphasize is that— there is no evidence that any other vaccines used in that season, or in any other season— can trigger narcolepsy. So you know in the United States and Canada where they use different brands of vaccine, there was no clear increase in narcolepsy cases. And in other years there's been no clear increase in relationship to the flu vaccine. So, as a general rule, I'm encouraging people with narcolepsy and you know, if they're wondering about what to do with their kids, I'm just saying get the regular vaccinations. Because this was a really, really isolated problem. Specific to this brand, Pandemrix. and I

know of no evidence that any of the other routine vaccinations, or the yearly flu vaccinations, or for that matter any of the new COVID vaccinations, are capable of triggering narcolepsy. Now, of course anything's possible, but— at least thus far there's really no clear evidence to raise those concerns.

Julie: Dr. Scammell, what would be some of the other environmental factors— that could trigger, you know, I have the— DBQ0602 marker, as you know, you helped, obviously— I think that's one of the first things you did, was look at that. But then I don't personally know my environmental factors— what other things are possible.

Dr. Scammell: Well, there's been some research suggesting that just— very mundane things, like strep infections, might actually be a trigger. And so for instance, if you look at the levels of antibodies against strep— they tend to be higher in people in the year or so after they develop narcolepsy, suggesting that they might've had a strep infection that preceded the onset of narcolepsy. So this is— these are, we're talking here about spontaneous— people who just spontaneously develop it. Nothing to do with vaccinations. But if you just take a bunch of kids with new narcolepsy, sometimes— there's evidence that, hey they had strep recently. And of course you say, well, kids are always getting strep. But you can compare them to age-matched kids, and the levels of antibodies are still higher. Other than that, we don't have any other evidence for specific triggers— however there is kind of a seasonality to onset— so in China where there's lots of people, and pretty good tracking of cases, at least in the big cities— it does seem that— the onset of narcolepsy is more common in sort of the period from March to June. Suggesting that maybe if there's this lag of a month or two, maybe— maybe some winter infection? Uh, was a triggering event.

Dr. Scammell: The thing that's kind of frustrating about that is, who knows what the trigger is, right? There's so many, just winter infections that are normally floating around. But on the other hand you could sort of say, well you know what— there's really no way to avoid these things. And so, at least at the moment, lacking any specific— known triggers, I don't encourage people to, to stress about this too much. It's just— you got to live your life, and— not worry about the triggering things.

Julie: Yeah. Though I think people always try to, like— it's, its— probably human nature to try to look back and be like, well what could've been? [Laughing] You know? Even if there's nothing to do about it, necessarily.

Dr. Scammell: Yeah. And Julie, when you developed narcolepsy, do you think there was any— can you identify anything that might've preceded it?

Julie: One of the only times when I think it got worst pretty quickly, I did have two severely decayed teeth, and I had to have root canals on them— and I think I've— I don't know if I've ever asked you if that could've been an infection— that could've, somehow caused— I don't— what do you think about that? [Laughing]

Dr. Scammell: Well, I mean I think in that case— Yeah, I mean your immune system is fighting off the inflammation around those teeth, right. And so your immune system was kicked into gear for some reason. And— maybe? Do you think it worsened your narcolepsy, or do you think it preceded it?

Julie: I think my sleepiness started when I was in college— in like an— abnormal way— and this would've been my junior year, between my junior and my senior year of college. And it's one time when I just really remember it feeling a little bit worse.

Dr. Scammell: Ah, yeah. You know you raise an interesting question, of— after the first few months of symptoms, does narcolepsy get worse? Right, I mean it's— if somebody has moderate sleepiness, a year after the narcolepsy develops— is it possible that they might get worse over time? And we don't actually have a whole lot of evidence for this— there is a smattering of research suggesting that at least in a small number of people, orexin levels in spinal fluid can actually fall over the course of months or years— after the onset of narcolepsy. But in your case, that you raised the question of like, might an additional— immune activation — actually kill off a few more of those neurons. And I suppose it's possible. But it's— again it's not something that we— know anything about right now, and its not something one can plan on or avoid. But, but— in general, my usual feeling is, is that— most people sort of, develop you know, plateau— in their narcolepsy symptoms within a few months or— or that first year.

Julie: Okay. That's interesting, 'cause I always thought my sleepiness probably started around 18— but then my cataplexy and hypnogogic hallucinations were when I was 21. Very distinctly. But I don't think the sleepiness I experienced at like 18 or 19 was norm— like, was average— you know, so. But I don't know.

Dr. Scammell: Some of this stuff may also be the brain adjusting— to the loss of the orexin neurons too. That it, the brain is trying to compensate and then weird stuff happens, and so for instance we— are working with some mice— right now, that we developed. Where, we can acutely kill off the orexin neurons, and within one week, the mice are super sleepy. They don't get any worse after that first week— but they don't really develop full blown cataplexy until six weeks later. Um—

Julie: Oh, wow!

Dr. Scammell: And so theres something weird that happens— the orexin neurons are dead and gone— but then the cataplexy lags way behind.

Julie: Wow! That's really interesting!

Dr. Scammell: So, yeah. It may be that some of the symptoms that we see are not— directly a consequence of orexin neuron loss, or orexin peptide loss— but rather, they're a response to how the brain is trying to adjust. More on that later.

Julie: Yeah. And I— so I think, that you raised another really important thing which is kind of a question I hear a lot from people, well— you know if you had a type 2 narcolepsy diagnosis for — 10 years could you all at once spontaneously develop cataplexy at that point.

Dr. Scammell: Mm. It does happen occasionally. It's unusual. If you follow those people, and Dr. Mignot has a nice paper on this— a pretty good number of them, like maybe 25% of those people who start off— without cataplexy— but have low orexin levels, about 25% of those people will develop cataplexy eventually, but it can take years. And so it's possible that— again, maybe there's some ongoing loss of orexin neurons, or maybe— it's just the brain adjusting to that situation. But, yes— type 2 narcolepsy occasionally does evolve into type 1 narcolepsy.

Julie: Of course there's also cases I hear of— of, someone being asked, like— oh, do you collapse over? With emotion or— do loss of muscle tone. And someone will say, no, I don't do that! And uh, not realizing until they hear, more— from other people living with narcolepsy and cataplexy, like— oh— so it could be that I just lose my smile, you know, when I laugh, or— just a little bit of my jaw or my eyes fluttering— so, its really, I mean I'm sure that for this they really

draw it out, who really has cataplexy or not, but it is interesting how— it's still hard for people to even understand sometimes— when they're being asked about it.

Dr. Scammell: And this is where working with a doctor who's— who knows narcolepsy well can be very helpful, so that they're asking the right questions because— yeah, no, if you only ask— do you fall down when you laugh? You're going to miss a lot of cataplexy. Sure, that happens a bunch— but, I think for every episode of full-blown, fall-down cataplexy, many people have 10 times as many partial episodes. Where, as you say, your face goes slack, the eye lids close, their head bobs forward, their speech gets slurred— stuff like that.

Dr. Scammell: This is a little more detail than most people might care for, but— we'll just— I'll try to get through it quickly.

Julie: No, you have the science nerds here! It's good, it's good!

Dr. Scammell: It's— some little— creepy crawlies, we can call them pathogens, alright. So those are bacteria and viruses. Your body's always fighting these, every day. You're fighting off various invaders like this. And there's these cells called antigen presenting cells, or APC here. Which are basically these little things that gobble up these— pathogens. And they chop them up into little bits and kill the bacteria and the viruses. But— that's not enough to have a good immune response, and so what they do is they take those little snippets, of broken up bacterial proteins, and they— send them to the outside of their cell, where they're presented by these— its called MAC class 2 cells— thats actually the HLA molecule that we talked about for the 0602— they take these little chunks of pathogens, the little pieces are called peptides— and they stick them on their outside, bound to this MAC class 2 molecule. And they show them to what are called T cells, the CD4 cells. And the CD4 cells then make chemicals that can help kill bacteria called cytokines— and this whole network together, can help kill off infections. So, the bacteria get chopped up, little bits of them get shown to the T cells, the T cells get activated, they release cytokines that kills the bacteria. That's the normal situation.

Dr. Scammell: This is what we think might be going on in narcolepsy, which is that some of these T cells then cross into the brain, across this thing called BBB— blood brain barrier— and, it turns out— that some of those T cells are cross reacting with something expressed on the orexin neurons. And so these cells, even though they— I'm going to say, "think", that they're killing off a virus or a bacteria, they're actually targeting the orexin neurons and they kill those cells too. So its sort of a question of accidental molecular memory. Where the molecules look similar but they're really on your native orexin neurons.

Julie: What're like the next steps of figuring out the process? Like what are the biggest— unknowns?

Dr. Scammell: Yeah, well one of the things is— you know, it's all fine to say that there's T cells that cross react with these orexin neurons, but are they— truly— are they the killers? That's one thing. We need to find sort of the smoking gun, here. Because if it's— if it really is those T cells, then maybe can do something— to influence the activity of T cells. Like for instance, there's drugs that can prevent the movement of T cells across the blood brain barrier. It keeps the T cells outside the brain— and they don't get into the brain, and so— um, if you were to— catch somebody early enough, when they're just— beginning to develop narcolepsy, maybe you could give one of these drugs, to help prevent the T cells from getting in and killing more orexin neurons.

Julie: Is there any research around trying to find other ways to measure hypocretin? Because it sounds, I mean the spinal tap is— pretty invasive, and so I remember when you diagnosed me

you said, well there's— you know, there's probably not likely many hypocretin or orexin left, and— its not really worth it. There was no big question for me, but— do you think that that's— any, you know— would that be helpful? If we could better measure that, easily?

Dr. Scammell: People who have such clear narcolepsy as you do, the test— the measuring orexin in spinal fluid isn't really necessary because the other evidence is so strong. I think it's— I think its more useful in people where I'm kind of wondering, it's like, is this really cataplexy? Something's a little odd about this story— or, huh— this is weird, this person doesn't have the gene that we would expect them to. You know, that kind of stuff where the pieces don't line up in the normal way. That's when I think it's very nice. And actually you know that, probably the most common circumstance is— people with narcolepsy have a higher prevalence of depression than the general population, so its not unusual for somebody to come into clinic, on anti depressants and maybe their depression is substantial enough they can't stop those medicines— and yet anti depressants mess up the multiple sleep latency tests, and so— we can't really do a proper multiple sleep latency test when somebody's taking anti depressants. And so, if somebody's depression is fragile enough, that we don't want to stop those medicines— a spinal tap's a very short path towards getting a clear diagnosis of type 1 narcolepsy. People would love to have a blood test. The thing that's tough is that, while a tiny amount of orexin may leak out of the brain into the blood stream, it probably gets chopped up pretty fast. And there's a few papers that claim to have measured orexin in blood— but, I actually think they have a lot of technical problems and I'm not convinced that this is— really working. Birgitte Kornum, a researcher in Denmark, has a fairly recent paper on this, where I think she's getting some measurements, but you have to do it in a very particular way. And— [laughs] —most importantly, what they're measuring when they measure a tiny bit of orexin in blood— it's just— [laughs] —it's not any different in people with narcolepsy or healthy individuals. And so while there may be a tiny amount of orexin in the blood, it doesn't reflect the deficiency of orexin in the brain. So I'm not holding my breath for a blood test any time soon.

Julie: Okay, alright. [laughs]

Dr Scammell: I know, I wish— I wish. But and maybe there'll be some other sort of more indirect markers of it but I think a blood test is not imminent. So we've talked about how narcolepsy's caused by a loss of the orexin neurons. So how does that then result in sleepiness? And so, here's a human brain. It's just kind of cut right down the middle— and so up top you can see the cortex, at the bottom you can see the brain stem. And in the middle is where the orexin neurons are. The hypothalamus, and that's where the orexin neurons live. Normally, the orexin neurons send strong connections to lots of brain regions that help wake you up. And these make neurotransmitters that you might've heard of before, like— acetocholine, histamine, dopamine, serotonin, norepinephrine. And these are found all up and down the brainstem and hypothalamus. And so, under normal circumstances the orexin neurons help turn on these other types of neurons, which then help keep you awake. But what we think is going on is that in the absence of orexin, the activity of those target regions is just inconsistent and so they're not releasing histamine and dopamine and serotonin like they should. And it— and what that results in is sleepiness, where people can easily lapse into episodes of sleep. And, also if you're— if you don't have enough, for instance, norepinephrine and serotonin, your REM sleep's going to get kind of weird too. So the way we're thinking about this now and it hasn't been proven yet, is that— it may be in normal circumstances, norepinephrine, serotonin, etc, stay at nice high levels while you're awake through the day, but — if you don't have orexin— those systems are kind of flickering a little bit. And they're not releasing the neurotransmitters as consistently, or to the same extent as normal. And so— that could be the cause of the sleepiness.

Julie: We had a guest when we were talking about napping, I guess— he's a pediatric sleep doctor who also has narcolepsy, but he talked about how, you know— we often think of like, narcolepsy as— like, kind of what you're saying, that it's a loss of wakefulness, as opposed to — somehow the sleep drive was— was talking about the wake versus sleep drivers. And how its really the loss of the— is it the loss of the wake drivers as opposed to the sleep driver somehow getting stronger, right?

Dr. Scammell: Great. I think that's a super important perspective on this. And its that, I think that fundamentally the sleepiness of narcolepsy— is about poor maintenance of wakefulness. That, that— that normal— consistent alertness that most people have, just doesn't really work so great in narcolepsy. And so it's a problem of keeping, the normal systems that— that help keep you alert— they're just not working right. It's kind of like, it's kind of like a city that doesn't have enough electricity and you have these brown outs. Where you're just not powering things adequately, and so you have these lapses into sleep. In contrast, my intuition, and there's not a lot of evidence for this— is that idiopathic hypersomnia is kind of the opposite problem. It's not a problem with staying awake, it's a problem of waking up. And so that's why a lot of idiopathic hypersomnia people have a heck of a time waking in the morning, and they can sleep for 12 hours at night. But once they— once they're awake, they actually can generally stay awake better through the day than somebody with narcolepsy. They're not lapsing into sleep quite as frequently as— as someone with narcolepsy. Um, but yes, I think— the phrase that we use all the time is, poor maintenance of wakefulness in narcolepsy.

Julie: I like that, 'cause I think it's also important to remember, like that— its not always falling asleep, like that's what a big thing I always talk about is that people think, oh are you falling asleep right now? And I think its partly from, you know, movies— but to realize how invisible sleepiness can be, is that your eyes can be open but you could be on another planet, or not remembering what's happening, and all the cognitive— yeah.

Dr. Scammell: And so, as an example, so maybe— I'm just making this up— but maybe that's your norepinephrine neurons— lapsing— but some of the other systems are still kind of going, right? And so, you're literally not running on all cylinders, if that makes sense. Right? It's enough— it's, it's like, in a car, you know— in an old car, if one spark plug fails, the engine actually can still run, even with 3 cylinders firing, right. It's not running well but it's still running. And so I think you could imagine a similar scenario where there may be sort of lapses in one or the other of these neurochemical systems. Not enough to make you fall asleep, but certainly enough to impair cognition.

Julie: Hmmm. That's interesting, I like that.

Julie: I know there are probably a lot of other questions, I was just curious— I really do feel like orexin, you know we knew about the loss of hypocretin orexin— 20 years ago, now— over 20 years ago? 20 years ago.

Dr. Scammell: Mm-hmm.

Julie: It seemed for a while that there was no interest in, um— or very little interest in developing treatments, and, but I was wondering if you think that possibly— as we learn more about hypocretin and that there could be other— I mean— or orexin, I mean the system has to do with more than just narcolepsy, too, right? And if any of that research is of interest. Not for necessarily for narcolepsy but, what else is orexin being look at for?

Dr. Scammell: Right. So, um, boy thats a big question. So I think you might know, that there's now several pharmaceutical companies that are interested in designing drugs that mimic the

effects of orexins. And, um and the hope— is that, they will really improve alertness and help suppress cataplexy in people with type 1 narcolepsy. But, your question's a good one, in that well, you know, everybody's got an orexin system, and so what's it doing most of the time? And it's actually kind of surprising, we don't know a heck of a lot about that. I mean, you could look at the other symptoms that sometimes show up, like you know, there's more obesity, mood can be down in narcolepsy, there's— other stuff that doesn't get as much attention as sort of the major sleep symptoms. And who knows, it's possible that some of these drugs that influence the orexin system might be helpful for other problems too. Like maybe they will help with mood, maybe they will help with weight loss— back to, getting back to a normal weight, that kind of thing.

Julie: I feel like there's also research in drug abuse?

Dr. Scammell: Yes, yes. And this is actually, gets even more complicated. So, the current drugs that are being developed, target— so there's two receptors in the brain for the orexins. They're called OX1 and OX2. And OX2 is the one that seems to be most important for promoting wakefulness and regulating REM sleep. OX1 maybe has more to do with some of the potential drug abuse pathways. We call them reward pathways in the brain and if you activate these, animals find it rewarding. If you give an animal a drug that can be abused, like opiates or amphetamines, it activates these reward pathways and, so— it's possible that a drug that activates the orexin 1 receptor could actually be a little bit of trouble, in the sense that it might— have some addictive potential. And the hope is that a drug that targets the orexin 2 receptor may be less likely to do so. But again, this is really early days and the truth is, orexin 1 and orexin 2 receptors are expressed in lots of different brain regions and there's a lot of overlap— and so, I think at least for research purposes, some day it would be really nice to have drugs that target each of these very selectively.

Julie: Yeah. I just think it's interesting 'cause, you know, when people talk about rare disease drugs and— I wonder if orexin— if it wasn't for narcolepsy, you know, would orexin have been discover— I mean maybe at some point.

Dr. Scammell: Well— well, you know. Orexins were discovered before the connection to narcolepsy was even known. But— I think the research on this whole system has certainly been accelerated by the strong disease connection. You know, it's much easier to get research funding from the government if you can say, we're doing this to try to help people with narcolepsy.

Julie: Oh, okay. Alright.

Dr. Scammell: So, we've got the orexin neurons. And normally they would be connecting to some of these dopamine neurons in the brainstem. And dopamine is a really important system in these reward pathways. So there's quite a lot of research now, suggesting that orexin activation of dopamine neurons enhances rewarding behaviors. And— and actually the strongest evidence comes from animal research, when they give a drug that blocks— the orexin 1 receptor— mice are much less likely to abuse— amphetamines, cocaine, opiates and things like that. And so it seems that, an orexin blocker might actually help in drug addiction. And now there's the beginnings of some clinical research along those lines. So, if orexins normally enhance activity in these reward pathways, then what happens in somebody with narcolepsy, where there's less orexin. Well, maybe those reward pathways are not as active as they should be. And maybe the consequence to that is that— things that should normally make you feel good and be rewarding, just don't give you quite that same thrill— and maybe that results in some depression. That's just speculation on my part, but I— in a very sort of broad sense— maybe, a loss of orexin, excitation of the dopamine system, can depress mood.

Julie: I— I always wonder about these, and I've probably mentioned this to you before, Dr. Scammell— about whether when we are asking people, on the clinical side, if they have a depression diagnosis along with narcolepsy, whether it's ever clarified that— that could've possibly been a misdiagnosis on a way to a narcolepsy diagnosis, and how much that's parsed out. Just out of curiosity because it seems that depression is one of those, when we say it's 8-15 years for average, and many people are never diagnosed— it's one of the things that was suggested to me that could be happening, before I found that I had narcolepsy, so. Is that ever — parsed out?

Dr. Scammell: Well, I think that this is where— I think this is yet another reason why there's such a delay in diagnosis. Why it can take a long time, because— depression is really common, right. I mean, there's way more people with depression than there are with narcolepsy. And so, if you go to a primary care doctor or a psychiatrist and you say, "Ugh I'm just so tired, I can hardly get things done— I'm not doing well on my classes—" they're going to think depression first. Because that's common. And that's no fault of theirs, and the unfortunate thing is many docs just aren't familiar with narcolepsy and so they don't ask the next questions. Right? And so, somebody with depression would say, "Ugh— I just can't get out of bed in the morning, I'm not getting anything done, and maybe in the afternoon I get a little bit done." But somebody with narcolepsy would say, "Oh I actually feel pretty alert in the morning, and I get my best work done then, but then at two or three o'clock in the afternoon I just crash and burn and have to take a nap." Right it's a very different feel— but it depends on how— how you probe into the person's symptoms. And so, I haven't seen any sort of research on this but I wouldn't be the least bit surprised, if— in people who truly have narcolepsy, I wouldn't be surprised if depression is sort of, one of the wrong diagnoses— that gets tossed around prior.

Julie: Thank you, that's what I— that's always my curiosity, 'cause— yeah. I don't know. And, when people do genetic testing— and they send off like their spit or something, would something like that ever come up?

Dr. Scammell: If you just did like, 23andme or something like this.

Julie: Yeah.

Dr. Scammell: I don't know if it shows up on that. We send it as a special lab test, and my guess is that 23andme and that kind of sort of non-specific genetic testing doesn't drill in with that level of detail. But it's a lab test that can be done pretty much anywhere. So, the gene again is called HLA-DQB1*0602. Cataplexy is super interesting, right, I mean how is it that laughing would actually make you fall onto the ground, it's literally the just— nuttiest thing imaginable. And so, we're starting to put together the pathways, and this is— how we think it goes— is that, first off— you got to perceive that something's actually funny, or surprising, or novel, or whatever it is that triggers your cataplexy. So that's something up in the cortex. And we think that the medial prefrontal cortex is important. Normally, the medial prefrontal cortex would excite neurons in the amygdala— the amygdala's an emotion regulating area. And they also excite the orexin neurons. Well the amygdala sends— inhibitory projections to this area in the brain stem. This brain stem region normally helps suppress REM sleep. And, so the amygdala— reduces activity in that area, and the orexin neurons would normally increase activity— so they kind of balance out, but if the orexin neurons are gone, then the amygdala is unopposed, and what we think happens the— those positive emotions are routed through the amygdala, they then— that then turns off this area that is supposed to be putting the brakes on REM sleep, but is not now, because the amygdala's turning it off— and so that allows for increased activity in brain regions further down that promote REM sleep. And when we say

REM sleep we're talking about the paralysis of REM sleep, really. And ultimately that inhibits the neurons that control your muscles— the motor neurons. So, there's a lot of steps in this, but the idea is that— something that you perceive as funny or novel, triggers emotional pathways— those emotional pathways mess up the REM sleep regulating pathways in the brainstem, and then before you know it the motor neurons are inhibited, and you get weak.

Julie: And so is this some of what you're working on?

Dr. Scammell: Yeah, we're doing a lot of this stuff in mice. We've been focusing on the amygdala for the last several years now, and we— we're trying to figure out specific types of neurons in the amygdala. Because if we could figure out like, oh— it's this very special type of cell— then maybe, we can, you know— help develop drugs that can help influence the activity of those cells without doing a whole lot of other stuff— um, and target cataplexy more specifically than some of the current drugs.

Julie: Also just wanted to thank everyone for your advocacy because, some of what Dr. Scammell works on is funded through federal grants, right. And so we're really, really grateful to all the advocates that are working so hard on making sure that sleep disorders research gets funded through NIH and um— so, you know, it's not ever an exact pathway, that one person took action and it led to something like Dr. Scammell getting research funding— but it's an important part of the process, so it— it's cool that we're all here together, and get to, you know — see some of your, your work. And try to understand it— it's tough for me, this stuff is a little bit— [laughing] tough for me to quite understand, but. Yeah. So just thanks for everyone for taking part in that process as well. Thank you Dr. Scammell so much for taking this time today to be with us. Thank you everybody!

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