Prof. Dirk De Ridder: " The concept that I, as a medical doctor, whether I'm a neurosurgeon, psychiatrist, neurologist, or whether I'm an audiologist or psychologist, treating tinnitus patients by ourselves cannot work and will not work, and if we do not change, it will stay a problem forever. If we use the same technology and approach as they do in sports, high-tech sports, then there's no reason why we should not be able to conquer this probably within 5 to 10 years."

00:00 Introducing Dirk De Ridder

Hazel: Today I'm here with **Dirk De Ridder**. Dirk, welcome to the **Tinnitus Talk** podcast. It's lovely to have you here. Would you mind just briefly introducing yourself to our listeners?

Dirk: I'm Dirk De Ridder. I was born and raised in Belgium where I trained as a neurosurgeon to become interested in brain surgery for tinnitus, which was part of my PhD project, which tried to develop surgical brain surgery solutions for tinnitus, and then in 2013 I moved to New Zealand where I teach and do research, not only related to tinnitus but related to brain stimulation and brain modulation for a variety of pathologies such as pain, obesity, addiction depression, etc. but my main research topic is still tinnitus. And since a couple of years I've also set up a clinic back in Belgium where whatever we develop as novel treatment modalities in New Zealand is then immediately translated to the clinic so that it's not just sitting in an ivory tower and developing new theoretical models and new treatments but those innovations are also immediately translated to a clinic.

Hazel: Right, and I think we should probably talk a lot more about your clinic and also how those other conditions that you've researched and are interested in, like pain and depression, might or might not be related to tinnitus, but maybe first can you explain how did you first get interested in tinnitus as a neurosurgeon? I think that's interesting because there's quite a few neuroscientists who are studying tinnitus, but neurosurgeon, that's a very specific specialty and I'm curious to hear how that led you to become a tinnitus researcher.

Dirk: Yes, so unlike many other tinnitus researchers, I don't have tinnitus myself, so it's not a way to treat myself, but I got interested in tinnitus because my preferred surgery was microvascular decompression surgery, which means that if there is a blood vessel that taps on a nerve inside the brain that can cause symptoms—and usually those symptoms, such as pain or vertigo, respond very well to that kind of surgery, and it happened to be my favorite kind of surgery, and then when I thought, well, I would like to research and start a PhD, then what is the worst outcome associated with this kind of surgery, which was tinnitus. And so the practical reason was that I thought I could make a difference by investigating how we could improve the surgical results of removing or detaching the nerve from the blood vessel from the auditory nerve and thereby improve the tinnitus. Consequently, because it is a very rare cause of tinnitus, I had to start understanding the general mechanisms and pathophysiology behind tinnitus and that's how I rolled into researching tinnitus as a whole and not just this one rare cause of tinnitus that could be treated in a surgical way by my preferred kind of surgery.

Hazel: What was it about tinnitus that sort of, I don’t know, really piqued your interest?

Dirk: From a brain perspective, my ultimate goal in life is to understand how the brain works and tinnitus, for me, was similar to phantom pain, and phantom pain and phantom sound from a purely theoretical perspective appeared as something that could be studied in a relatively easy way, and being a little bit arrogant in the beginning of my studies, I thought, well, we'll solve the problem within five years, and then we'll study something else, but it has shown to be a lot more complicated than I ever imagined, even though from a practical point of view, the phantom sound should be more easy to tackle than, for example, personality disorders or post-traumatic stress disorder or depression or other pathologies that we encounter in clinical practice, yet it has shown to be resilient to even aggressive treatments, which, as neurosurgeons, we tend to sometimes propose, but that being said, it has helped tremendously in gaining a better and fuller understanding of how the brain functions, and so my main interest is the interaction between how the brain creates phantom sounds and phantom pain as a way to resolve inherent uncertainty in a changing environment, so it has grown really into a quest of how the brain works and functions within the environment that ultimately create the brain.

06:41 Traditional and contemporary ways of thinking about the brain

Hazel: Why do you think tinnitus has proven to be a more persistent problem than you had initially imagined?

Dirk: I was trained in a very old-fashioned way, in which the brain was conceived of as a passive absorber of information from the environment that would process it in a specific place—so in one spot in the brain would be responsible for one aspect. So for example, there would be only the auditory cortex that will generate tinnitus. It was a very simple concept and then the solution is very simple. You just suppress that over activity in the auditory cortex and the problem is solved.

Yet we now know that there are two problems with this approach. First of all the brain is not phrenological, meaning the brain is not built in such a way that one symptom or one thought is created in only one spot of the brain, but that the brain ultimately creates emergent properties from networks. That being said, if you put all the pieces of a car together in a very specific way, you get a functioning car; if you don't put them together in a very specific way—so if you don't connect all those pieces of a car in a perfect way, then the car won't function, and it's the same in the brain. So tinnitus needs to be seen as an emergent property of connections between different parts of the brain, which is of course very more difficult to tackle than just one spot in the brain that generates tinnitus.

And the second problem with the way I was taught is that the brain is not passive in absorbing sound information from the environment, but the brain makes predictions and then actively goes and explores the environment for the predicted sound. That being said, if in the past, for example, your brain has processed always specific frequencies and because of hearing loss you don't sense those frequencies any more, then the brain will say there is something wrong and we should be better safe than sorry, so I will fill in the missing information from what is stored in memory related to this specific context, and the problem is that the brain will generate the sound just to be on the safe side to reduce the uncertainty that is increased by not hearing that sound—and that means that it's the prediction error that creates the sound.

So these are already two very different, novel approaches to tinnitus that we were just not trained to take into account, and, of course, these two aspects: first networks and the prediction that the brain does, has revolutionized the way most neuroscientists now look at brain functioning and because this is new, we had to completely rethink the way we approach tinnitus. This has made it very exciting but also very frustrating because we've tried many many things based on the wrong model basically just like at one station in history people thought the

Earth was the center of the universe and then Galileo said, “Well, I don't think that's correct; it's the sun that's at the center.” Well, this new way of thinking about the brain is of the same difference as the geocentric and heliocentric approach to the universe.

10:42 How our understanding of the brain has evolved

Hazel: Yeah, that's really interesting, and I don’t think many people realize just how fundamentally our understanding of the brain has changed and evolved in the past few decades, and here’s even—and I still hear, for understandable reasons, I hear other tinnitus patients say, “Well, can't they just find the part of the brain that causes the tinnitus and then you just like zap that part and (*laughing) it’s fixed?” So, but what from what you just explained it’s, you know, there's this whole new understanding that it's not the case that this part of the brain does this, that part of the brain does that, but it's much more a complex interaction within and across brain networks, and that's that's what makes it so complex, I supposed. And then I think the other aspect, and I’m really just trying to summarize it here for my own understanding as well, I think the other aspect you mentioned was that the brain is not a passive processing machine of the inputs that come to it, including auditory inputs, but it plays a much more active role in how those inputs sort of manifest because it makes predictions and those predictions draw memory and other things. So am I sort of summarizing a little bit the challenges here from a lay perspective correctly?

Dirk: Yes, yes, this is correct, but it's also beautiful because this creates a completely new way of not only looking at the brain but also at looking at the environment and looking at what's happening around us in the world, and it makes a lot of sense. From a practical point of view, it takes us about three hundred milliseconds—let’s say close to half a second—before a sensory stimulus is turned into a conscious perception. If we would not predict what is going to happen, we would be running half a second behind and time consciously, which is impossible to survive. I mean we would run every time we cross the street we would be dead because the car would be there by the fact that we can predict the car will be at a certain spot one if we make that step that allows us to survive in a very—in a changing environment and so prediction is already embedded in the most basic living creatures, for example bacteria can predict not in one generation, they need 10 generations to be able to predict the very simple cellular creatures like amoebae or the slime mold, which is a very intriguing creature where multiple cells, when the going gets tough, combine into 1 unit. They can predict already within one generation, which means that this addictive capacity from an evolutionary point is essential in order to adapt to a changing environment because if you can predict what's going to be behind a rock, whether there will be a predator or a partner to mate with, will allow you both to survive longer and also to procreate, so it's essential for sexual and natural selection. It's a fundamental aspect of nature that we have not really used until relatively recently.

14:34 Where tinnitus originates: the ear or the brain?

Hazel: So let's maybe take a step back because we've sort of dived into the tinnitus model and your theory of how tinnitus comes about already, but let's maybe take a step back and I'll ask you a very basic question about how tinnitus arises, and that's the ear versus the brain question, which, I think, you know, again, there has been some evolution there over time in scientific understanding of where tinnitus actually originates, but I still think there isn't consensus probably about this, and so I'm interested to hear like why do you emphasize the brain so much and why do you see tinnitus primarily as a brain disorder, even in those many cases where it is caused by hearing loss or some kind of ear trauma.

Dirk: Well this is a very good question because actually the tinnitus has already been described in the **Ebers Papyrus** which goes back three thousand years, and it was called bewitched ear. So tinnitus was linked to the ear and actually this continued until the 1990s, where tinnitus was considered an ear problem and then **Jastreboff** suggested that the brain was involved, but until 1999—actually until 2010—tinnitus was considered an ear problem.

Now if tinnitus is an ear problem then the solution is easy. You wear a hearing aid and the tinnitus should improve, which unfortunately is not the case. Only 20% of the people who wear hearing aid do get better. That being said, if the simple solution to the simple concept that tinnitus is an ear problem would be correct and everybody should improve. Therefore, we had to consider that there is another aspect that is more fundamental. and then an American—a Colombian American neuroscientist and zoologist, **Rodolfo Llinás**, was the first to suggest or show using magnetoencephalography—basically recording magnetic activity in the brain—that the auditory cortex was involved in tinnitus, but that is only 20 years ago and the essential component of that is that ultimately it is not the hearing loss that is important but how the brain responds to the hearing loss. If the brain doesn't care that you have hearing loss, basically of the brain is certain enough that the missing information is not dangerous, then it won't create the sounds. So that is a very simple reason.

If the ear would be the cause for everybody, then everybody with hearing loss would have tinnitus, which is not the case. So from a very practical point of view, there was some problems with the theory that could not stand very simple logic and therefore we had to find another explanation, and then still in a very phrenological way was shown by Rodolfo Llinás that the auditory cortex was involved, and we all though, that's it! We just have to, like you said earlier on, zap the auditory cortex and we will quiet the tinnitus, which is what we did in the beginning and with some success. Some people benefit but not everybody and then the question is, okay,

well, if not everybody responds then we have to redefine the theory again. We have to—if we can't explain tinnitus improvement or rather failure by zapping the auditory cortex, then we have to find another explanation.

And then a young German researcher, **Winny Schlee**, said well, maybe we should just consider it as a network rather than a phrenological auditory cortex problem, but that was only in 2009, meaning that's very recent, so this then created another approach where we said we should not just tap or zap the auditory cortex, but we should maybe combine it with a stimulating other parts of the network and we knew that the frontal cortex was involved, so we started stimulating the frontal cortex and the auditory cortex, which was a little bit better than the auditory cortex all by itself, but still it was not good enough, meaning the theory was still not optimal and that's when **Rauschecker** a year later said well, if that doesn't explain I have the solution; it's not the input that's the problem is that the brain doesn't suppress it. It's a problem of the break on sounds and therefore the target again changed, so our treatments were always adjusted to the new theory.

The problem was that didn't work either, so we had to come up with yet another theory which was then the patient's brain concept which was the predictive model but that hasn't really led to any practical approach and we now just published a paper that says well, maybe it's both; maybe it's not just a lack—maybe not too much input that the brain creates but it's the balance between how much the brake works and how much the accelerator works and that's still creates novel treatment approaches, meaning that you have to compute the balance in the brain using imaging and then say well, we have to press a little bit on the break and let the accelerator go a little bit and that's very different than again one approach, so basically we learn through our failures of treatments and so the theoretical model of how tinnitus evolves in time is rapidly accelerating through all our failures. And this coincides with this novel understanding of the brain functioning in general that we discussed early on, and this is why we see new treatments develop associated with new theoretical models.

So from this point of view, to be honest, I don't care which model is the right model, the right model is the one that works, the one that will lead us to find a cure for tinnitus and that will be the correct model and all the models that we have developed in the meantime are just little stepping stones towards what you could call a unified model—just like the physicists are looking for the theory of everything, we should be ambitious enough to look for a theory of everything in the tinnitus domain so that we do not only treat the tinnitus distress or the the bother of the tinnitus but really get rid of the sound itself.

22:22 Current theories of tinnitus

Hazel: Yeah, I couldn't agree more. Where do you think we are now in that journey towards a unified theory because I think there's still a number of different theories out there. I think they're not necessarily mutually exclusive, so you also just talked about how, you know, two different theories and both could be true at the same time or something like that, but what's your assessment of where we are now and can you talk a little bit about the prominent Central Gain Theory? I think there's—it's actually a group of related theories, right? But what I think they have in common is that it's based on the presumption that when there's a loss of inputs that somewhere along the auditory pathway, I think, in the lower brain regions, I'm not sure, to compensate for the loss of input the gain or volume dial is sort of turned up to compensate. How do you look at that theory? Is it compatible with how you see tinnitus or not?

Dirk: Yes, so basically there are two big theories now. One says tinnitus is due to auditory deafferentation, meaning there is not enough input in the brain and the brain makes what is not coming in. That's one big theory and the other big theory is the **Rauschecker** model of the deficient noise cancellation, so one says the brain creates too much noise and the other one says the brain doesn't work. Now the gain theory is just one aspect of the deafferentation model where the claim is that well, if you don't hear very well, the brain will just make the auditory system more sensitive to input so that it can still pick up as much information as possible from the de-created or lacking auditory information.

Now from a practical point of view, this is a very engineering approach to a problem that is fundamentally just an explanation of how in auditory information the gain should increase. Now if the gain increases in every patient then you would expect every patient to have hyperacusis, meaning hypersensitivity to sound, which is not the case, meaning that the gain theory cannot be a unifying theory, because otherwise it should increase every sound input and then everybody should have hyperacusis, so that is not a fundamental theory in my mind; it's very valuable because we know that you can modify gain in the brain, for example by applying noise, so if you apply noise you can—and that's the beauty of electrical noise is that it can normalize both decrease gain and increase gain due to normal features, so the theory certainly has a lot of value because it makes a couple of predictions that leads to theoretical new treatment possibilities, but it is philosophically not fundamental; it's more an engineering approach to what we know is happening when there is less information coming into the brain.

25:57 Missing pieces from current theories

Hazel: So what's the missing piece here? You said gain doesn't explain everything. What's the missing piece in your view?

Dirk: I think the missing piece is that a lot of how we develop theories about the brain in involvement in tinnitus is based on still some static models even though they're network models. Now the brain is constantly changing, so the way we analyze data is we put somebody in a scanner whether it's an fMRI scanner or it's an MEG or EEG—it doesn't really matter. We average data over 5 minutes or 10 minutes and then we say that's the network. Now this, of course, is linked to the methodology, but it's a tremendous weakness because our brain constantly changes and so a couple of years ago, about 3-4 years ago, **Anusha Mohan**, who works in **Sven Vanneste**'s group showed actually that the network is dynamically changing, and interestingly that the auditory network is constantly on the lookout for information, so its flexibility is increased, which we thought was actually going to be the opposite; we predicted the opposite. We thought, while somebody hears "eeeeeeeee" all the time, so that means there is no change, so the auditory cortex should be very non-changing. Well, the data showed exactly the opposite, which, of course, is in keeping with the **Bayesian brain model**, the predictive theory, that once there is not enough information the brain goes and looks for information everywhere else in the brain, and if it can't find it from the outside, then it will just pull it from memory, so that was interesting

And the second mistake and our predictions we made was that we predicted that the distress would be associated with the brain being very on the lookout for, but it was the opposite. Actually this stress is caused by the fact that the brain focuses only on the sound and so thereby is not processing other relevant behaviorally relevant information, and by this zooming in or this focusing on the sound, that leads to the distress, so this dynamic changes of course we have to take into account when we develop new treatments.

Now then the question is why does somebody's brain change into a tinnitus network and someone else who has exactly the same hearing loss not? This is a fundamental question that we have not been able to unravel. **Jae-Jin Song** in Korea has very recently shown beautiful data that shows that the posterior cingulate is involved and this is very relevant because the posterior cingulate is a part of the brain, part of your self perceptual network that relates yourself to the outside world, so from a practical point of view, if your brain—and he's also using some other computer models where he's looking at entropy, meaning a lack of information—what the brain does with the lack of information and if you conceptualize his data, basically what it means, if the brain doesn't care that there is a lack of information, you won't get tinnitus. If the brain says this lack of information is important, then that will generate tinnitus.

Now why would the lack of information be important or not? That depends on the context. For example, if you've been tortured, sound during torture is extremely important, and so

everybody who was tortured with sound will develop tinnitus, because it is in the context, the sound is very relevant, whereas if you would develop tinnitus in a nice environment, let's say you go to a concert, for most patients, it will disappear because it was linked to something pleasant—if you like the concert, of course, and then that will not generate a tinnitus. That being said, if you develop tinnitus while you're in a divorce or why you lose your job or in a period of COVID, like now, the chances that it that your brain will say this is important, is higher, and therefore it cannot ignore it because the brain just says well, it must be important because it happened in this context and so whenever you get into the same complex that causes a problem. Then the question is why does that not happen with everybody, and so you can push the boundaries and then you have to start looking at something that has not been looked at in tinnitus whatsoever and that is epigenetics.

31:12 The role of epigenetics

Epigenetics means that you've got your genes, and we know there's certain genes that are involved in the generation of tinnitus; those genes are interestingly the same that are involved in pain, depression, sleep problems, hearing loss, so associated comorbidities of tinnitus, which means that also, if those genes are involved, the question, of course, is how much does everybody with those same gene problems or polymorphism—so the variants of specific genes can lead to tinnitus. Now only 6% of those who have those genes developed tinnitus, and so you can, then again, push the question one step further. Why does not everybody with those genes develop tinnitus, and that's where epigenetics becomes involved.

Epigenetics is basically an influence on how your genes are activated or not activated, and this depends on the environment. So for example, if you are very stressed or if you've been abused as a child or if you have a physical trauma or a mental trauma, that will create physical changes on your DNA; the DNA itself doesn’t change but you add specific groups, chemical groups on the DNA so that basically your DNA is ready to respond very quickly if the same situations occur again. So it's a way of preparing your DNA to respond to that stimulus, which means that if the DNA is ready to respond, to put it very simple, to create a network that generates tinnitus, then those epigenetic factors, meaning the same stress as you've had before, will again reinforce the brain, saying it is important and then the problem is it becomes chronic. But then the question is how does it become chronic? And the chronicity is what we can then learn from other pathologies, like depression, like anxiety, Alzheimer's disease.

Chronic pain seems to be related to a low grade neuroinflammation, so low grade inflammation of not just the auditory network but also the stress or suffering that works, so when they become chronically inflamed, that seems to lead to a chronification, and then it’s unsurprising

that the genetic and epigenetic factors are also involved in those products that are creating neuroinflammation and information transition.

So from a very practical point of view, there's two components. You've got your genes and you've got the environment. The environment changes the way how your genes are expressed and that's why not everybody with the same risk genes will develop tinnitus. If you have risk genes, then what will happen is that you're likely to get tinnitus from the first hit. If you don't have risky genes, then you can have these epigenetic modifications, meaning that normal genes can be expressed in a different way, and then if you have a second hit, that's going to lead to tinnitus.

So from a practical point of view, what we have to do is we should bring all that information together meaning the grey network, the genes, the environmental influences, and this create patterns that we cannot as a human unravel, and that's why we ultimately will need artificial intelligence to help us with this problem. And this is what we are currently trying to do is see, can artificial intelligence help to unravel the patterns or the links between genes, epigenetics, which ultimately is changed by the environment, to explain why there is such a variety and the imaging data or the brain expression or the brain networks that we link two tinnitus, and so the model becomes even more complicated, but it’s addressable by using ultimately artificial intelligence, the patterns and recognitions that we as humans unfortunately cannot find ourselves.

This is where, in the future, we will need large groups of people to collaborate, meaning creating European projects, American-Asian projects that look at data of maybe 1000-2000 tinnitus patients who have their complete genome sequence to have their epigenome sequence to have the microbiome sequence to have the EEG data and then apply all the pattern recognition of the artificial intelligence to ultimately tell us for this patient, for example, these three signal molecules in the brain are not optimal, so that we can supplement them and for this patient, actually these connections are not optimal, so that we can rebuild those connections or break those connections, and the beauty is that in the last couple of years new tools have been developed where we can try to rebuild connections and try to break connections, whereas before because our model was wrong, we were just saying, okay, well, this part of the brain, the auditory cortex is overactive, so we just have to suppress it. That's it. That's a very simple approach, but we did not have the technology to target different parts of the brain at the same time. Now the technology exists, but it's not yet used, still in an experimental phase to see are we truly rebuilding connections or are we truly breaking connections.

Once we know we can, then it's just applying the changes that the artificial intelligence will tell us that are typical for tinnitus—basically the signature of tinnitus, and so I do think that through technology, we are actually going to be able to individualize the treatments that we currently use. It will take a little bit; it will take five to ten more years, but that is just a matter of scaling up what we're currently doing, so the theoretical models are currently being built and the technology is being simultaneously developed, so it's just a matter of bringing those things together, but everybody will have to collaborate and we will need one or two people to organize the collaboration—call them team leaders whatever you want—that also know the clinical component of it, but the concept that I, as a medical doctor, whether I'm a neurosurgeon, psychiatrist, neurologist, or whether I'm a audiologist or psychologist, treating tinnitus patients by ourselves cannot work and will not work, and if we do not change, it will stay a problem forever. If we use the same technology and approach as they do in sports, high-tech sports, then there's no reason why we should not be able to conquer this probably within 5 to 10 years.

39:42 How to unify tinnitus research

Hazel: I think that's a very strong and inspirational call to action, and I really couldn't agree more. Of course, I'm a relative outsider but I talk to a lot of tinnitus researchers and my impression is always that it is very fragmented what is happening currently and often people don't even know about other people's research when asked about it, and I completely agree that what we need is kind of a big unifying project with a few people really leading the way. There has to be a vision like we're going to solve this problem in X number of years, this is what it's going to take. It has to be very multidisciplinary and there has to be large-scale data gathering and then, as you point out, with very sophisticated data processing capabilities with artificial intelligence, and yeah I would love to see that happen. How do we make that happen, Dirk (*laughing)? What do you think?

Dirk: You know the **America's Cup**, the sailing race, is run by private people, a couple of billionaires who spend loads of money on creating those extremely highly technological and highly sophisticated boats, but not the only the boats are sophisticated, in Team New Zealand, there is I think 12 Olympic medalists, so also the people that run the boats are extremely highly advanced. Now I've written a little text on the on the TRI, the Tinnitus Research Initiative website, where I suggest that actually what we need is the same thing; we need a competition where teams are formed and have they have built a treatment within a certain time frame, just like there is, on that day, there is a sale race, and at that time you have to have your product, and then it's just a competition of who builds the treatments that can benefit most people or that can reduce the sound most—in most people—of course you say there's ethical problems there because how are you going to test it on humans and how are you going to test it on?—

well, you can. That's why we have ethical committees. That's why we have—and there is no reason why just like the America's Cup normally is held every 4 years, or like the Olympic Games, why we should not be able to create competition of building the best treatments, whichever treatment it is that works, but if you do that, you have to create it just like the America's Cup or like the Olympic Games. It's—okay, well, there is a competition for neuromodulation devices. You build a neuromodulation device specifically for tinnitus. The problem is that we need the budgets; you need a large budget to develop what is required in order to be able to treat it, but from a conceptual point of view there is no reason why that would not be possible. If you have a group of my microbiologists and ethicists, people specialized in neuroinflammation, imaging people, artificial intelligence people, and you force them to work together just like they do in Team New Zealand, you force them to work together for a common goal with a deadline and a competition, then that should at least result in a lot of an innovative approaches because the competition will drive the people to come up with solutions that nobody else has thought of. So now our problem is—I have a very comfortable life, if I develop something new now or within five years, nobody cares. I still get my salary as an academic. If there is no pressure, no deadlines, no competition, then we will move too slowly. So I think creating a little bit of competition would be highly beneficial.

Hazel: I think we can call on the TRI for that.

Dirk: Well, I think we first need to call on some millionaires or billionaires to create a competition, where they could maybe even see the benefit of a commercial product—whatever because it has to be a win-win situation, just like developing—and if you do this for tinnitus, there's no reason why you could not do that for other medical problems, as well.

45:02 How tinnitus is related to self-perception

Hazel: Yeah, yes, I'm going to think hard about how we can push for this because this is an excellent idea, but I want to ask still a few follow-up questions regarding the pathophysiology of tinnitus, and then I want to move on to more clinical applications and talk a bit more about your experience working directly with patients. But on the pathophysiology and the brain networks, I watched a YouTube lecture of yours for a talk about how, when tinnitus suffering is maintained for a longer time, it becomes ingrained in a different part of the brain. I think it was the default mode network that you were referring to, which deals with self-reflection amongst other things, and in your words, then tinnitus becomes a part of who you are—that's how you phrased it, and you said it then becomes harder to treat, so we actually got a question from a listener about this; they wanted to know what you mean by that. How long does this process take and why is it then harder to treat?

Dirk: This is still a theoretical model, but we are looking now at imaging data to see if this can be supported or not, so the concept is that for your brain, if you have pain or tinnitus which is maintained for a while, that costs energy because the suffering activates normally the sympathetic nervous system, which is your fight and flight mode—that generates energy—about 30% more energy consumption than normally, which is dramatic.

Now biologically we are built to have as little energy consumption as possible because that's good for survival; if there is not a lot of food around, then if you don't consume a lot, it's beneficial, so what the brain then does is well, if I make this suffering of tinnitus the norm, the reference, then I don't have to fight, then I don't have to create the extra sympathetic activity anymore, create the extra energy as a response, so the only way it can do that is by integrating the sound into your self perceptual network, so the sound becomes part of your self perceptual network and this makes very clear predictions because the self perceptual network has been defined as overlaps with the default mode network, which is a network which is active in your brain when your mind is wandering, etcetera. That predicts that the longer you have tinnitus the stronger the connection becomes between your auditory cortex and your default mode network, and this is exactly what Jae-Jin Song in Korea has shown—that the posterior cingulate cortex, which is the main hub the central core of the self-representational network becomes linked to the auditory cortex and the lower hippocampus, meaning to the auditory memory and the auditory cortex.

Now if this is correct, then what it means is that you first have to detach those connections again. You have to break the sound generated by the memory by hippocampus auditory cortex PCC with whatever way you can, so we're currently doing studies now in New Zealand to see if we can break these connections with specific stimulation designs and medication. So, for example, we know that certain psychedelics, whether it's hallucinogens, like ketamine and MDMA, can break those connections specifically within the default mode network within our self-representation. That's also, of course, why if you have a psychedelic experience, you have the feeling that you're not in your body anymore, that everything is changing— that's because you have no reference.

49:25 How to break tinnitus connections

Hazel: Yeah, you can even lose your sense of self entirely in such an experience, which I think is fascinating.

Dirk: So what we're currently trying is—first of all to dissolve the self by psychedelics and then try to rebuild it without those abnormal connections, so that being said, what it means is that the model, the theoretical model, again creates the theory, the theoretical therapies. The

therapies link to the theory, so from a practical point of view, if this model is correct—that the sound becomes part of who you are, we have to dissolve who you are. You can do that with psychedelics, then you have to detach the sound network, meaning the auditory cortex, the parahippocampus from the self, which you can do by creating a noisy stimulation design so that it can't synchronize.

If that works, then that should be beneficial, but then you should still try to prevent this from reoccurring because if you have hearing loss, your brain might again try and do that, and that's why then, for example, you might need hearing aids, not to treat the tinnitus, but to prevent it from reoccurring or you might do mindfulness or whatever therapy that teaches your brain to basically say look, the lack of auditory input is not important because then you should not develop the tinnitus again. So, what it means is that if the tinnitus becomes part of who you are, you have to just take another treatment approach.

But it's doable, it's just creates a little—it makes it just a little more complex and it also means that you might have to work in different phases rather than what we do now. Now we still think well, we have to treat it all at once. In the future probably that won't happen. In the future we will think, okay, well, if this is correct, then we have to first detach the sound from the self, then we have to detach the sound from the suffering, which is still another network, and then we have to ultimately prevent it from recurring, and that being said, that will be two or three different sequential treatments rather than the one magic pill or the one approach that treats everything. It does take a different approach, but it's all doable because we better understand those networks and those connections, and we know which medications can work on which of these components.

52:24 Dirk's clinical work

Hazel: I would love to talk for another hour about this in particular, psychedelics, because I find that a fascinating topic, but I want to make sure we also get to talk a bit more about your clinical work. So you founded or co-founded a clinic called Brai3n, and I don't know how to pronounce it because there's a 3 in front of the 'n,' but I don't know how you say that, and I think before it used to be at 2, so, yeah, can you tell us a bit about how that came about and what you do in your clinic?

Dirk: So basically **Brai3n** with the '3,' stands for **Brain Research Consortium for Advanced International Innovative and Interdisciplinary Neuromodulation**. It's a lot of words, but basically what it says is that we created a clinic predominantly using neuromodulation, so brain stimulation, brain training, that is to be innovative and interdisciplinary. That was Brai2n. When I moved to New Zealand and Sven Vanneste, my long-term collaborator, moved to a university

in the United States, and Jae-Jin Song, who was a collaborator, moved to Korea, then we said, well, actually, now we're international, so we added the “International” and the third ‘i,’ so International, Innovative, and Interdisciplinary, and that's what the ‘3’ stands for.

So that's how Brai2n, which was folks local in Belgium actually became Brai3n, and so it's a collaborative effort and last year the University of Bonn also joined it, and why is this important? It is important because we all use the same technology; we all use the same methods of investigation, which means that we can pull the data together and also compare, so if somebody in Korea finds something then we can test it because we use the same tools and technology quickly in New Zealand or in Belgium or in Germany and each subunit has a specialty. So in New Zealand we do, for example, animal research as well as multifocal electrical stimulation research and in Bonn we will do invasive operative research as well as focused ultrasound because there's only two of those devices and in Germany and none in Belgium and none in New Zealand and none anywhere else. And then in the US and in Ireland, it is more focused on the cognitive involvement in tinnitus—how tinnitus can result in thinking problems and concentration and memory problems, etc.

So every unit has a subspecialty, but they're all research units and the Brai3n clinic just pulls the information from all these research units and tries to translate it as quickly as possible to the clinic, but only, basically once we have gathered evidence that it is beneficial. But the beauty is that we can do that before it gets published because sometimes it takes a year before something gets published, so once we have the statistical evidence that this approach benefits at least a group of patients, then it is justifiable to translate it to the clinic, and this is where the clinic in Belgium is trying to then also see well, it’s not because it worked in New Zealand or it worked in the U.S. or it worked in Ireland, that by definition, it will also work here. The goal is then to constantly evaluate whether what came out of research actually also is clinically beneficial.

And this is a little bit of a practical problem in the sense of how fast do you translate research data into a clinic. Some people will say, well you should at least have three, four, five studies that confirm before you apply it to the clinic. Other people will say no. If you have one study that is well done, well controlled, you can immediately apply it to the clinic. And there are people who are in favor—there’s a more conservative approach, and there’s a more proactive approach, and there is no gold standard for it. So it really depends also on the patients’ personalities. Some people will say no, no, just stay conservative, and others will say I’m willing for a more proactive—even if there’s only one study, that’s fine—I’m ready with this.

But it is a little bit more difficult than just having a clinic where you do routine treatments. And also it can be sometimes confusing for patients when they come in and then half a year later, we say well, actually based on the studies that we've now done, this might actually be better, so—, and that can come across as if we have no clue what we're doing because we're changing constantly. And we *are* changing based on constant better understanding of the pathophysiology of the treatments of tinnitus and the associated, innovative treatments, and because things move relatively fast now, both technology-wise and the understanding of the pathophysiology, I already know now that what we're currently doing will be different from what we're doing within six months or a year. But that's the way it goes, and I think it's only to the benefit of the patients—that we do not only have a hammer anymore because if you only have a hammer, everything looks like a nail, and then everybody gets the same treatment and it doesn't work for everybody.

59:20 Dirk's personal experiences working with tinnitus patients

Hazel: Yeah, and that's science, right? It's a continuous progression of knowledge, and I would say that the patient should be the key part in all of this, like you said, as long as they understand that certain treatments are experimental—I don't know if that's the right word to use, but if they understand that it's still early stages, and they are fully informed about potential risks, etc., I think that's the most important aspect of it. I can see how that sort of continuously poses some challenges. I'd love to hear more about your personal experiences working directly with tinnitus patients, and how do you go about making an initial assessment of someone's issues?

Dirk: The way we approach a patient is, if we can find a cause, we will try to treat the cause because that is still the most logical thing to do. Unfortunately many times we won't be able to find a cause and then you try to treat it in a stepwise approach, so for example, if somebody has hearing loss, then we will suggest to first try, if you haven't tried it yet, a hearing aid, even though if you look at meta-analytic data, hearing aids don't work. I mean that's if you pull all the data together from all the studies that happened on hearing aids, it clearly shows it does not work. But this is irrelevant to the patient. What I mean by that is for 20% of the patients, hearing aids work wonderfully well, but because of statistics, if you put all the patients together, those 20% are not powerful enough to statistically give for the whole group a benefit. So then the combined group has said, well, it doesn't work. And indeed it doesn't work for the whole group but it does work very well for a small subgroup, and so that being, you have about a 20% chance that you will really benefit from it; it's worthwhile to try a hearing aid. If the hearing aids does work, then that's fine.

If the patient has associated suffering—and this is mostly the reason why they come, because if you don't suffer from the tinnitus, you won't go and seek help—then we will often propose either medication just to treat the suffering, because suffering can be expressed in different ways. It can cause anger, fear, anxiety, depression—a lot of associated symptoms, then we will try to treat those, because if somebody is severely depressed or highly anxious, you cannot read the sound component at all because the brain is so focused on the sound component that it does not make even sense to try and treat the sound, you have to treat the depression or anxiety or the OCD-like behavior before you can treat the sound component. So then we first treat so that's the second step.

If the medication doesn't work or if the person says, look, I don't like medication, I want a non-medical approach, then we will use, in those patients, neuromodulation for the suffering, which means that we will use transcranial magnetic stimulation for which there is plenty of evidence that it can treat depression well, equally as well as medication or even better, for anxiety. If it is not severe, but it is still causing some suffering then we might use transcranial direct-current stimulation, which is an electrical form, but it's somewhat easier and it's also not every day; it's only two or three times a week, so it's a little bit easier.

And if that does not work, or if that does not benefit, then we will basically suggest to patients that we have recently done the research, and then this research has shown, but there is no hard evidence except for what we've done or what one group has done that this might benefit you, for example whether that is acupuncture or whether that is—it doesn't really matter as long as there is evidence that it has benefitted a subgroup of patients, then there is the options of doing those approaches.

So basically it goes from standardized approaches to more aggressive or more invasive approaches, but we start with the most easy, simple things, because it does not make any sense that I would use transcranial magnetic stimulation on somebody's brain if it's just ear wax in the ear. I mean, you start with the basics and you just build up based on what you find and what does not work basically. And so it’s a stepwise approach that unfortunately, will still not benefit probably 20-30% of patients who have no benefit. 60-70% of the patients might have a benefit, especially on the suffering.

Treating the sound component is still very very difficult, and this is where most of our research is still going on now because the ultimate goal should be to create silence not just to treat the suffering. Treating the suffering is an intermediate acceptable goal, because if you don't suffer from it and you can live a normal life, that's fine, but the goal should be to create silence.

1:06:06 Silence should be the ultimate goal

Hazel: I would agree, but I'm curious to hear more about why you think that's the case because, you know, if you talk to a CBT (Cognitive Behavioural Therapy) practitioner who treats tinnitus patients, they're likely to say, well, if we can remove the distress through therapy, then that is as good as a cure, right? So I think it really matters who you ask and what professional lens you're looking through, and this is quite a controversial topic. It's kind of, no matter what you say about it, you're going to make someone upset, but I agree that just removing the distress is not enough, and one of the reasons I think that's the case is because we can't remove the distress for everyone, right? There's going to be, like a group of patients for whom...

Dirk: And because you mention CBT, there is a lot of evidence, even meta-analytic evidence, that shows that CBT is beneficial for tinnitus, but like you say, it's for the stress; it doesn't do anything on the sound. But if you look at the data, it's statistically significant, but is it clinically very relevant? Because ultimately with CBT at a meta-analytic level, the patient has a 10-point benefit on the TFI (Tinnitus Functional Index) score. Basically 10% benefit. Now, if you just put it in numbers and your suffering is 80%, you go from 80% to 70%. I don't know if that's clinically beneficial because after 1 week, the patients say, well, yeah, maybe I'm better, but I'm still suffering 70 out of 100, instead of 80 out of 100, and that 70 will become the new 80, so I don't think that we can claim that there is any treatment out there that truly works. It's statistically significant but most, even those for which there is meta-analytic evidence, like CBT, only improve the patients by 10%; that's not good enough.

And just saying, well, we can treat them, we can cure them by giving them a 10% Improvement is really not putting the barrier high enough to come up with new treatments. And if we as clinicians are not our biggest critics ourselves, and if we get satisfied with our results, there will be no advance anymore. As long as the goal is not to create silence, then we should do something else, then we should just say, well, we're not tinnitus specialists. You might be a psychologist or psychiatrist, and that's fine. If your goal is to treat the suffering, then you should say I'm not a tinnitus specialist, I'm a psychologist or psychiatrist; I treat suffering, mental suffering. If you claim to be a tinnitus clinician, then the goal should be to create silence, otherwise there is no reason why you should call yourself a tinnitus specialist.

1:09:13 The pros and cons of medication to treat suffering

Hazel: Yeah, I would tend to agree. I'm curious to hear a bit more about what you said earlier—that you can't proceed with more sophisticated treatments until you reduce the distress or anxiety and that you believe prescribing medications for that can be a good step. As you pointed out, some people are hesitant also to take those anti-anxiety or antidepressant

medications, particularly long-term. What's your view on that? Do you really see it as just a short-term measure just to sort of break the cycle and be able to intervene more effectively, or can it be used longer-term as well?

Dirk: Yes, I think it can be used longer term, but you have to be careful in the sense that, for example, SSRIs (Selective Serotonin Reuptake Inhibitors), which are very often prescribed for tinnitus actually can worsen the tinnitus; they can improve the suffering, but they can worsen the tinnitus, so then the question is what are you really doing? So a lot of antidepressant medications, actually as a side effect, can generate or worsen the tinnitus which is present and so then you create a vicious circle where you have to keep on adding medication, which worsens the tinnitus, which can then—so that's not a good option.

But there are a couple of medications that can be taken, but like everything, the goal is to treat the tinnitus for at least two to three months, because that's more or less, to put it simply, how long it takes your brain to rewire a little bit. So from a practical point of view, after 3 months you try to taper, if it has a beneficial effect. If it has a beneficial effect after three months, you try to taper the medication to the lowest dose that gives a benefit. Ideally, no medication, but if you can't, then you can take the medication, and this is a new approach that I would not have done a couple of years ago, but is putting more responsibility in the patient's hands. For example, you can say, taper it down, but if you feel you get anxious again or you start feeling depressed, take it for a couple of days and then, again, you stop, so that you can tailor it to the need of your brain, basically, rather than enforcing a status quo, and the reason why you would prefer that to giving a constant medication is because if you give constant medication, your brain will adjust to it and if your brain adjusts to it, then it just kind of ignores the medication, and then it has no benefit, so you want to also minimize, but not stop if it's needed. And if they have to take it for the rest of their lives, they have to take it for the rest of their lives—but at the minimum dose that gives them a clinical benefit.

And why would you do that? Well, for example, as I mentioned people with neuroticism have the same genes as people with tinnitus, and people with pain. Neuroticism is one of the characteristics that drives or that creates a higher likelihood that if you have tinnitus, it will become chronic. Now, what does it mean? It just means that those people with neuroticism are more stress sensitive or less resilient, and therefore they will start suffering more than anybody else. It's not that they are weaker, it's not that they're mentally weak, it's just the way the brain is wired. They will start suffering quicker, so you can then stop the medication, but no one beforehand that the person like that will, within 3 months, be back at full scale where he started, which does not make any sense. Then you might have to take it for the rest of your life,

whereas if you are, let's say a person with—you're a musician—they're hyper focused on their sound.

Often it's just very disturbing for musicians, but it depends on the kind of musician. If you're a classical musician and you're obsessively focusing on the purity of the sound, then the interference is a problem. However, 60% of rock musicians have tinnitus, but it's rare that it bothers them because it's part of—well, they played when they were young without any hearing protection and it's part of it, but actually it's linked to something positive—to the fun they had on the stage, and therefore it does not seem to bother those rock musicians as much as it would bother a classical musician, a violinist who strives for the purity of one stroke because they're it will interfere and it will be perceived as something very negative. So in those two people, two kinds of musicians, your treatment will be different, and then one, if the rock musician has the problem, he might just need a very short treatment for whatever causes a worsening of the tinnitus—let's say, getting divorced or whatever, then you treat that and then afterwards they are fine. Whereas if you have a classical violinist who has some OCD-like features, you know he will have to take or she will have to take medications for the rest of her life. So I'm not in favor and not against anything; it just depends on what is necessary.

1:15:26 Transcranial Magnetic Stimulation

Hazel: Right. Yeah, it makes sense. You next mentioned, I think, transcranial magnetic stimulation, and I think you previously said that this gives positive results to only about 20 or 30% of patients but maybe that was a few years ago. Do you still believe this to be the case and then how can we improve those numbers?

Dirk: Initially we were using transcranial magnetic stimulation on the auditory cortex. As you mentioned earlier on, we zapped the auditory cortex because we thought that's where the problem is. We quickly realized it did not work, and in the beginning there were heated discussions whether you should go contralateral to the side of the tinnitus or always on the left side, but the fights we were having were useless because they were missing the entire point that it was not a good treatment for tinnitus. So now we use transcranial magnetic stimulation not to treat the sound but to treat the associated depression and anxiety, which you see in about 20% of the patients and especially those who come to the clinic because they suffer, so if they have clear-cut anxiety and depression, and we define that based on questionnaires and on the psychiatrist who works in the group and a psychologist who works in the group—if they have clear-cut depression, we will treat them with transcranial magnetic stimulation if medication in itself does not work, but often we use a combination because it has been shown, for example, that if you combine transcranial magnetic stimulation with medication that the benefit is bigger than medication alone or stimulation alone. So we use the combination to

treat first the depression and it depends if the patient says look, I can now live with the tinnitus; there is nothing else—there's nothing else—sorry (*phone ringing), so we often combine transcranial magnetic stimulation with medication because it has shown that medication plus magnetic stimulation works better than medication alone or stimulation alone. If after this treatment the patient says well, now I can perfectly well live with it, this is fine, then there's nothing else that needs to be done, but we don't stop all at once.

We taper the stimulation so instead of doing everyday stimulation we go to once every 2 days then once a week then still once every 2 weeks just to not stop the treatment all at once. But we don't target the auditory cortex anymore, and even though some patients might still have a little bit of benefit for the sound component, we're now currently focusing more on melty target stimulation to break the network in order to truly make a difference. This is still experimental, so we're not using it yet in the clinic, but those studies should be finished in six months and maybe in six months we will use that in the clinic, so yes, we still use magnetic stimulation but for the anxiety and the depression because most studies actually do show that for the sound component it is not sufficiently beneficial. It's very costly; it's not reimbursed, and therefore the chances that somebody benefits from it are, in cost-benefit analysis, not high enough to warrant its routine use and clinical practice.

Hazel: Right. So currently, what you can offer is mostly treatments to target the distress and that the treatments to target the tinnitus itself are—that's why you're doing the research, basically. That's still under development.

Dirk: Yes.

Hazel: Yeah, okay, what's your opinion on some of those bimodal neuromodulation devices that are out there; there's the Lenire® device, there's dr. Susan Shore working on a similar type of device, do you think those also only target the distress, or do you think they are effective enough?

Dirk: Yes, they only treated the distress, even though the claims will be different, and the reason is very simple if you treated the distress, the sound was also the decrease a little bit because what the distress does is—if your brain must stress is a mechanism in which your brain says everything is important. Now if everything is important the game will change, so basically a sound will become heightened and its experience, the pain will become worse, the tinnitus will become louder. If you treat the distress secondarily to that, the loudness will decrease a little bit. It won't disappear but it will decrease a little bit because the game is normalized.

Now, that being said, the concept in itself is not abnormal because how does the brain function in daily life? In daily life, what the brain does if you talk to somebody, you will not just listen but everybody will lip read, and based on your lip reading and the sound your brain will say well that's the word that was mentioned, so it's our brain constantly uses what is called abductive reasoning, meaning if it sounds like a duck, it flies like a duck, if it behaves like a duck, it's most likely going to be a duck. So that interaction between vision and sound and sensation is logical, and the problem however is that it is no better than any other treatment that treats the distress, so even though in a study, like in Susan Shore's study it showed that it also dramatically decreased the loudness, but the moment you stopped, the loudness was back, so you can't constantly keep on doing the stimulation with the Lenire® device.

They never published the loudness benefit, only the distress benefit, and the distress benefit was lasting, but the problem is if the Lenire® device does not improve the loudness, then it becomes difficult for us as clinicians to know when we should use it because while we can also treat distress many other ways, the distress in general can be treated by the magnetic stimulation, electrical stimulation, mindfulness treatment, CBT— there's many. And then it becomes difficult to see what you should offer to a patient, so if the patient, of course, says well, I strongly believe this should help me, that's fine. But still you should try and guide somebody and say well, have you tried maybe simple hearing device. That might already be sufficient or we can also give you a medication for two or three weeks that might benefit you, or we can do TDCS or we can do Lenire®.

And as long as we do not know which is a subgroup that benefits from these kind of bimodal stimulations, it becomes just another hype like we've seen many coming by and this is some— a little bit of a problem is that because there is no good treatment yet whenever something is publicized or mediatized then many patients want it, only to realize that again, it works in 20-30% of the patients really beneficial and 20-30% of the patients it has a little bit of benefit, and in 20-30% of the patients it doesn't do anything, which is unfortunately what we see with most of the treatments that we currently do. And that's why research is still very important because whatever we can provide now works in 20 to 30% of the patients.

1:24:31 Will hearing regeneration help?

Hazel: Yeah, so it's not really a meaningful improvement in that sense. One other thing that is hyped up a lot in that sort of online tinnitus communities, including **Tinnitus Talk**, is hearing regeneration and a lot of people seem to believe that would, if we can restore hearing—which by itself is a huge challenge and would be a huge breakthrough—if we can restore hearing, then we can fix the tinnitus, and I tend to be a little bit skeptical about that. I was curious what you think.

Dirk: Well, I think hearing improvement would be a dramatic benefit. The question, however, is as we've discussed earlier on, at the moment that the tinnitus becomes part of who you are, even improving hearing might not benefit. Also, if hearing improvement would be the goal and the magic, the holy grail or the magic bullet, then hearing aids should have a lot better effect than they do have now. Of course, you can say while the hearing aid does not increase the frequencies above 8000 Hertz and they are the most important, etc., etc.

But hearing regeneration, and there is currently trials going on, to my point of view, might be especially beneficial for preventing tinnitus to come back after you've created treatments, which of course would be very good because that's a—even if you take psychedelics and you can detach the sound from the self, and you can then prevent the hearing loss, then you should have a good treatment. Maybe one, two, or three sessions of psychedelics just like in post-traumatic stress disorder where they combine ecstasy with psychotherapy, and within three sessions the post-traumatic stress disorder patients do not seem to qualify anymore according to the criteria of post-traumatic stress because the way they look at their trauma is like as if they look at it from it from a movie or it's detached from the emotion.

If that is possible for tinnitus that would be highly beneficial, so we're currently setting up a study where we will use the same thing; we will use ecstasy with sound therapy. Now just imagine this works; the tinnitus is gone then the problem is, if the hearing loss is still there, it might come back after a while, and so if you can regenerate hearing to a functional level, then that might prevent the tinnitus from coming back, so I do believe there is a future for it, but maybe more as a prevention rather than a—it will certainly not be a cure all. Just look at pain, chronic pain. Some patients after surgery develop chronic pain. Most do not. Those who develop chronic pain are just like in tinnitus, they have a specific genetic profile, they have specific environmental factors that have been translated by epigenetics and to chronic neuroinflammation, but it's not because you restore sensation that pain appears. So I would not hype it to the extent that it would cure everybody because as we've discussed before there is at least two groups of tinnitus: one associated with hearing loss, the other one where the break does not work. If your brake doesn't work, and you improve your hearing, it won't make a difference. So, that being said, it will be an advantage but certainly not a cure all.

1:28:35 Other potentially promising treatments – neuroinflammation

Hazel: Are there any other new treatments or developments out there that you think are particularly promising?

Dirk: Apart from the psychedelic approach, the chronic neuroinflammation approach with—so if we can prevent this chronic inflammation from continuing, we should be able to stop the chronicity, and apart from the multifocal stimulation network approach, so, where you stimulate the network and the preliminary studies of hair cell regrowth, I'm not aware of anything else that is or that could at this stage revolutionized the treatment approach, but even though—while the four approaches I've just mentioned in itself should offer a lot of hope for people who suffer from tinnitus, maybe not one but the combination of different approaches might ultimately be the goal because of how you treat and that work is by using a combination of different approaches, and this is insufficiently done, so we know for example when people got—when AIDS in the beginning was treated, originally, there was only one drug, Azidothymidine, and patients were benefiting from it for a while, but now with four different drugs, they've basically—I'm not saying they live a normal life, but their life expectancy is fairly normal, so they're never cured, but it's controlled. And it's controlled by attacking the network from different sides simultaneously.

This is still what we have to learn in the tinnitus field where we still, and to be honest, I make the same problem, is that we say, well, the problem is if we do four treatments at the same time, we don't know what works. Well, that's correct so what we do now is we do treatment A. If it doesn't work, we go to treatment B. If that doesn't work, we go to treatment C, and etc. This in itself might not be good, just in the AIDS treatment, the benefit is in the combination of the approaches and that's what we should in the future go to. The problem, however, is that it is more difficult to study from a scientific point of view. It's easier to do one, to test only one thing, so scientifically it's a little bit more difficult. But ultimately for the patient, science is important, but the clinical benefit is even more important—how how they can benefit—and we might have to accept that maybe the science might be somewhat less rigorous, but that ultimately the goal is two-fold: it's 1, to understand the mechanisms better because that will allow us to develop better treatments but on the other hand the main goal still has to be to treat the patient.

Hazel: Yeah, which kind of brings us back full circle to something that we were talking about earlier, the need for this grand-scale project that combines lots of different approaches and with large-scale data gathering, etc., so let's hope we can get that off the ground.

Dirk: Yes, and I think the most easy way of doing it would be for a group of people to sit together and tap into some European money or the tinnitus research initiative, especially under influence of **Winny Schlee** has already been very successful in getting some grants, European grants, to create an academy where young investigators, PhD students, are enrolled, so the momentum is there but it's still at the investigational approach. I think we should maybe

conceive of the next phase of European money to go to a real treatment approach where we go away from this one phase then the second phase to a network approach with multiple different concepts as we've mentioned before. Genotyping everybody, epi-genotyping everybody, microbioming everybody, EEG-ing and then just have the artificial intelligence help us in determining the patterns that we know should exist but that we are incapable with our human intelligence to extract from the data.

Hazel: Do you think we could use, to some extent, existing data in biobanks because we're working on a project together with some academic partners to sort of map existing biobanks and whether they contain tinnitus data or which other data they contain, like neuroimaging and lots of different data points. Do you think that could be an approach that could work?

Dirk: Yes, certainly. I think it's an intermediate approach because the problem of the biobank is there was always missing data in the sense that the tinnitus might, for example, be just a question: do you have tinnitus or not. Is it a pure tone? Is it noise-like? Is it left? Is it right? Is it— so, the biobanks are very good, and I think it's a very good first approach, but if you really want to tackle it, then you have to have more specific data than the biobanks tend to have.

1:34:00 Wrapping up

Hazel: Makes sense. Yeah, so Dirk, I think we need to start wrapping up. This has been just hugely educational and informative for me. Is there anything that we didn't talk about that you still want to touch on?

Dirk: Not really, I think that we've covered a lot. What we probably have not covered is the association of tinnitus or the link or the similarities between tinnitus and other pathologies that can help us to understand tinnitus better, and, of course, the best known is phantom pain and phantom sound. That is obvious. Maybe we should also look beyond that and ask people how we could benefit them. You can call crowd signs or whatever it's called, so together with the Technical University in ___ we've set up a program where people who have tinnitus can put information in the database and then using symantec artificial intelligence we want to extract what benefits them, rather than the ideas come from researchers, the idea can come from the people who have tinnitus or who have conquered or benefitted their tinnitus.

They can say, look, for me this seems to work, and if the database is big enough, then that might be a novel approach where the crowd knowledge might actually become very helpful in developing novel treatments, so involving people with tinnitus again creating a databases where you can then extract patterns from—whichever pattern that maybe—can help not only

to elucidate further the pathophysiology of other correlations or pathologies, but also maybe find very simple remedies that we haven't really thought of because we only have a hammer and everything looks like a nail.

Hazel: (*laughing) This brings me to a whole other topic that we are also passionate about at **Tinnitus Hub** and **Tinnitus Talk**, which is citizen science, and we have a number of projects in that area and I think we're also uniquely well-positioned to gather data online from a large group of people. The last survey we ran last year got almost 9000 responses, so usually when academics hear that they're like yay, those are the sample sizes we need! So we're always actively looking for collaborations in that area, so maybe that's something we can connect on another time.

Dirk: With pleasure.

Hazel: So, Dirk, I would like to thank you so much for spending so much time with us today. I hope it was as enjoyable for you as for me.

Dirk: It certainly was.

Hazel: All right. Thank you.

Dirk: And have a nice part of a beautiful day, as it is today.