00:00 Introduction

Hazel: Welcome to the **Tinnitus Talk Podcast**. I'm Hazel, your host, and I can't believe this podcast has been around for over four years now. We are probably not the most prolific podcasters, but I believe we've been consistent and prioritized quality over quantity. Over the years, we've interviewed some of the most well-known tinnitus experts, and focused particularly on the science behind tinnitus.

Today, we have a special treat for you because we're revisiting with the very first guest of the podcast, **Dr. Josef Rauschecker**. He's a well-known tinnitus researcher, a neuroscientist, and as far as I know, the only person to ever have delivered a **TED Talk** on tinnitus, which is, by the way, very well worth viewing on YouTube.

When I first spoke to Josef, and you can go back and listen to this in episode one of the Tinnitus Talk podcast, it's still very interesting content today, he explained his theory of how tinnitus arises in the brain. He calls it the gating theory, because it's based on the idea that people with tinnitus lack a mechanism, or a gate, so to speak, to filter out neural noise from the auditory system.

It's still one of the predominant theories today. In this episode, which was recorded in person by yours truly at Dr. Josef Rauschecker's office in **Georgetown University**, Washington DC, we speak about why he still believes his theory to be true, how this could be translated into treatments, why he thinks we should focus a lot more on testing existing drugs that might work for tinnitus, rather than developing new ones, how tinnitus and sleep are related, what he thinks of psychological approaches to tinnitus, why animal models on tinnitus often fail, and lots more. Just a reminder that if you value our work, you can support us through Patreon. Our work is volunteer based so your donation will go directly to covering our expenses. Just go to https://moretinnitustalk.com to find out more.

And now, I proudly present the interview that I recorded while visiting Dr. Josef Rauschecker.

02:23 Explaining the 'gating' theory

Hazel: Josef, thank you for talking to me again.

Josef: Pleasure.

Hazel: We're here in Georgetown, where you work. In fact, we're in your office, so thank you for welcoming me here.

Josef: Yeah, I'm really glad that you made it all the way from Europe and well, from... ARO is I think where you're coming from.

Josef: Exactly. Yeah. I was at the **ARO (Association for Research in Otolaryngology)** conference in Florida.

Josef: Yeah, so that's not too far away but...

Hazel: It's not too far. In the global scale, not too far, yeah.

Josef: It takes an effort. And thanks very much for that. So my interest, as you remember, in tinnitus began a long time ago. It was **Pawel Jastreboff** and **Jim Snow**, who ran the **Tinnitus Research Consortium**, who kind of recruited me, because I had written an article about neuroplasticity in tinnitus, I think it was 1999, so a long time ago. And I was becoming interested in tinnitus as a form of plasticity, a reorganization of the brain; more for basic science reasons, but of course, I realized that there was a lot of potential in clinical terms as well. And then I actually started to have tinnitus myself, so that's another motivation.

Hazel: Yeah. Your interest kind of changed.

Josef: Yes, yes, yes. I never got it really bad, it's still there in a kind of mild form off and on, and the off-and-on thing has always interested me, and that has really led to that theory that we've developed that tinnitus is not always there. If it was just a lesion induced plasticity, as I called it at the time, which has been described in a number of paradigms in monkeys and in other animal models where the brain reorganizes as a function of deprivation and plasticity... if that was the only cause of it, then it should be fairly stable. It should always be there and it should always come about when people have hearing loss, for example. But that's not the case. Only a certain subset of people actually get tinnitus when they have hearing loss. And it is definitely related to hearing loss, there's no question about that. But we think it's not the only reason. There's got to be something else happening in the brain that is sort of a gating mechanism that allows the hearing loss to cause the tinnitus and determines also maybe how bad it is.

Josef: But there's this other factor, and we did these studies in the late, well, it was 2010, I think, when we got the paper in **Neuron** that was kind of a breakthrough where we developed the whole theory on what's going on. And then we also found some experimental evidence was published the following year also in Neuron, where we showed that particular brain regions are also changed when people have tinnitus, severe tinnitus. And those regions are in the limbic system, **ventromedial prefrontal cortex**, subgenual region, which is known for causing depression or being involved in depression. And that kind of opened this whole door of a new attack on that disorder. And certainly you could call tinnitus in a way a mood disorder, as depression is to some extent.

Josef: And it changed the equation in the sense that some people were aware of that. They knew about all this, but they thought this was the consequence of the tinnitus. If you have this kind of nasty noise in your ear all the time, of course, you would get depressed. That was the logic. And we kind of turned the argument around and said, well, maybe what if both of these factors are contributing, and it's not a really causal relationship in one way or another, but it is somehow the combination of the two factors, the hearing loss and the change in the limbic system, that gives you that disorder?

6:56 Tinnitus disorder

Josef: Now, in the meantime, the field has moved on, and there's a now clear distinction between tinnitus and tinnitus distress. So there was a sort of consensus article that I'm also an author of, with **Berthold Langguth** and **Dirk De Ridder**, who put this together with a large number of authors. And we kind of agreed that this is really something one has to distinguish. Some people have tinnitus and they're not bothered by it at all. They couldn't care less. There's this kind of buzzing noise in their ear, but otherwise they live a normal life, whereas others are very severely distressed and they're on the verge of suicide. So we have these two extremes, and it is really the bother that we have to address, that we have to understand. And that's where I think we are on the right track, and we've done imaging studies now, that you know about and that we've talked about last time, and we're continuing those studies. This is still our main tool to dissect the brain and say, this is where something is unusual and this is something that may change in chronic tinnitus. I don't know. This was sort of the summary that you wanted me to give.

Hazel: That was the summary, yeah. Okay, so taking a step back, and people can listen to episode one of the **Tinnitus Talk Podcast** if they want the details, but your theory has for a long time been, just to oversimplify it a lot: There's a noise coming, a signal coming, from the auditory pathway, from the lower levels of the auditory pathway, which is typically caused by hearing loss, but there could be some other type of injury. And then in most people, that noise wouldn't be picked up by the higher brain regions, so you wouldn't consciously hear it. But your theory is that in people with tinnitus, this gating mechanism, whatever it is, that filters the tinnitus out from reaching the conscious levels of the brain, that mechanism is broken in people with tinnitus. I think that was your statement, to put it in layman's terms...

Josef: That's tinnitus in a nutshell, that's exactly right.

Hazel: Yeah, exactly.

Josef: And the hope was that we could pin down that exact cause, that deficit that happens in the limbic region, this gating system, and then fix it in people with tinnitus. Turn the knob a little bit and then it would disappear. That's sort of the dream that we're still dreaming, and it hasn't changed that much in terms of theory. I think it's still the same.

9:31 Recent insights from MRI studies

Hazel: Yeah, you still generally hold by this theory, right? Has it evolved in the past few years?

Josef: Well, as I said, we've done more imaging studies in humans and are finding more detail. It's become more refined. There are other brain regions now that we can add to the list. So far in the old studies, we had the **nucleus accumbens** as a very prominent region as part of the striatum, the **ventral striatum** that is important for mood regulation and stuff like this. And then there's a number of other regions that we think is important, and that's been confirmed, more or less. We've done resting state, functional connectivity studies, which are really high resolution, and it's not a difficult technique. People just lie in the scanner for a while and let this... They don't do anything, basically. They don't have to listen to anything. It's a resting state. And there is very consistent finding that in tinnitus patients, it looks a little different from the controls.

Hazel: Yeah, so I read one of your recent papers where you found that people with tinnitus have a higher volume of gray matter in the cortex. Am I saying it correctly?

Josef: Yeah, yeah.

Hazel: And you corrected for a lot of other things, like age and hearing loss, which we know that in some of the older studies in tinnitus, people didn't used to correct for hearing loss, so it's great that that's being done. But even after correcting for those things, you saw a clear difference between people with tinnitus and people without in terms of the volume of this gray matter. Can you talk a bit more about that and how it pertains to also your gating theory, does it prove or disprove the theory?

Josef: Yeah, that study that you're just mentioning, that's a follow up from one of our original studies because there was a need for revisiting this and because other people weren't able to replicate it. And I think people are actually buying more and more into it because they realize that there is something else besides hearing loss that must be happening. And there's these daily variations that people see. They're under stress, and the tinnitus goes up. Everybody knows about this, and so what is that? That's something we need to pin down and fix.

12:06 Psychological treatments for tinnitus

Josef: And some other people, like **Jennifer Gans** and a few others, use **cognitive behavioral therapy**, for example, and they're actually quite successful in fixing things like that. So one could argue, okay, even if we don't understand the exact nature of the brain changes, there's something that tells us that there are maybe what you call cognitive or psychological changes that you can somehow treat. And Jennifer makes the argument, well, as long as it doesn't bother me, it doesn't really exist. So we have to learn to live with it and say, okay, it's just a normal part of life, and it's something that we shouldn't get too upset about. So this is a way to deal with it too.

Hazel: I have to say it's an argument I've heard more recently. You mentioned this tinnitus disorder paper that you were a co-author of, and many tinnitus researchers who were also at the ARO. I heard various tinnitus researchers talk about, well, we should focus on the tinnitus distress, not per se the tinnitus itself. I'm a little bit skeptical. Maybe you can understand from a patient perspective why I'm little bit skeptical about that. It kind of feels like moving the goalposts a little bit, right? We weren't able to figure out this tinnitus thing, but let us then just focus on the distress aspect, because that is at least something we can understand and we can treat. Which I do understand, but you could also argue, well, we still have to fix the tinnitus itself.

Josef: I agree.

Hazel: Because we cannot treat the distress in everyone.

Josef: No, no, I agree with you totally, as an engineer that I am originally, we actually have a new center for neuro-engineering, where we're also interested in fixing tinnitus as engineers. Like I said, with this gating theory, you think there's something wrong, and you go and take your screwdriver and fix it. This is the engineering approach. And I would still like to do that, but it is reassuring, I have to say that we find these changes in the new tinnitus studies, in the resting state studies, for example, also the diffusion tensor imaging studies that are in those regions that Jennifer and others who do mindfulness studies and so on, treatment, also would put in that same domain, you know? So, in a way what we are doing is trying to give **mindfulness** treatments and mindfulness studies a neurophysiological basis. And I think this is where the two approaches meet, that we are saying,

okay, there's something to it, apparently, to these cognitive behavioral studies and treatments. And if we find the neurophysiological basis of those therapies, then we're in business.

Josef: And we're actually in a much wider sense in business because we can, I think it is desirable as a neurobiologist to find a neurobiological basis of these cognitive therapies. I think it would. Maybe they don't agree with me and they say, well, as long as it works, it's fine. But I, as a neurobiologist and engineer, I would say, I do need to know what is actually changing in the brain, including in tinnitus patients. So, I think I both agree and disagree with you on that. I think we can make progress by finding neurobiological basis of these forms of therapies that work at least in some people.

15:49 Animal models to cure tinnitus

Josef: The other thing that I want to mention, and you encouraged me to say that, is that we need animal models. And we have had one paper out since we last talked. Which was on monkeys that we treated with **salicylate**, and salicylate causes tinnitus, reversible tinnitus, in both humans and animals. And we saw that it works in rhesus monkeys, and it's reversible there. And we were able to test whether they actually had tinnitus by using an eye-blink paradigm. You know, so there's a well-known effect that hasn't been used very often, unfortunately, in the field. But people with tinnitus have a reduced threshold in terms of eye-blink. And that is true for human patients as well as for animals.

Josef: And so, we published that together. The human findings and the monkey findings confirm each other. And I think it's a first step towards establishing a different form of animal model that could go a long way. Because after all, primates are closer to us in terms of brain organization. And there are lots of old monkeys sitting around in primate colonies. I've talked to **Gregg Recanzone**, for example, at **UC Davis**. The **California Primate Center** has large colonies of monkeys that are reaching the end of their lives. And it would be wonderful to do these tests on these aging primates. And I think this is another direction that I'd like to go in.

Hazel: Yeah, we talked about this on the podcast, I recall, because you commented that the vast majority, it's probably 99 point something percent of animal models for tinnitus were conducted on rodents and others small animals that don't really have the higher brain regions, or not much of it, as humans do, right? So hence, your wish to use primates. And maybe we should clarify also because when people think of animal testing, and particularly on primates, they might think that you're torturing those poor primates. From my understanding, you're doing tests that you would also do on humans, basically, right?

Josef: Yeah, exactly. So the next step would be to do imaging on primates, which we can do and is totally non-invasive. And so this is, I'm glad that you mentioned that as well, that's an important point. Ultimately, whether we have to do invasive studies, that's a totally different decision, and we'll be facing that, perhaps. If it is worthwhile, we'll have to get permission from the **Animal Care and Use Committees** and the **NIH** and all those authorities. But ultimately, we'll see whether the imaging studies will be sufficient to clarify that.

Josef: But there's been a lot of animal studies on rodents, studying supposedly the effects of tinnitus. And as you say, the nucleus accumbens, for example, is one of them, those nuclei are very, very small in rodents. And that would profit from our primate model, for example. And there's also... it's involved in addiction and there's a lot of literature on that, that has been collected in primates, for example, and I think we would be, tinnitus would deserve, I think, to have the same kind of models that are probably more effective, ultimately, and are more closely related to the human disorder.

Hazel: Right. So what you've done so far is, I think, develop a behavioral test of tinnitus in primates? The next step would be the MRI studies. And what would you hope to find there?

Josef: Well, the time window when you do salicylate studies is, of course, very short. You can only do a few days until the effect goes away again. One would have to see whether one needs another model for tinnitus in terms of loud noise exposure or something like this, which is the common cause in most cases in human tinnitus. But there, again, the animal protection argument is, of course, very important, and we'll have to see whether this will be permissible. But I think it should because it is for the good of mankind. If we can find a cure for tinnitus, as I still want, this is still the goal. We all want a cure for tinnitus, not just a sort of understanding of it. We want to use the understanding towards developing a cure. And so I think if that's the goal, then we should also consider maybe more invasive studies in animals.

21:04 Speeding up new treatments

Hazel: Yeah. And ultimately, of course, human clinical trials, testing treatments. Can you speculate a bit about, based on your theory, what types of treatments should work in humans? I think you mentioned at the time something like **deep brain stimulation**. Could you give us some idea of what the treatments could look like?

Josef: I also mentioned that in my **TED Talk**. Towards the very end of the TED Talk, there's this example of a depressed patient who got really great relief from her depression by deep brain stimulation. It's a neurosurgical intervention, obviously. So you actually have neurosurgeons.

Hazel: This is quite invasive, you're saying.

Josef: It is invasive, yeah. But it's now a pretty well-accepted and feasible technique. And actually, I've been invited by a very big and important neurosurgery group in San Francisco, who also does studies on speech and language with these approaches on epileptic patients. They have now a clinical trial on their way where they study depressed patients with deep brain stimulation. They have a region in the... Well, not the nucleus accumbens, but it's sort of related to these areas in the subgenual, sub colossal area that we've also identified. And they've seen very encouraging results. And the idea is now to stay with these patients and ask them whether they also have tinnitus. As you all know, there's a high comorbidity rate between depression and tinnitus. And so we would restrict ourselves to this group where there's overlap between tinnitus and depression and see whether the symptoms of depression get milder or go away, that tinnitus also goes away. And that would be one sort of first steps.

Hazel: So you could use that study that's already ongoing.

Josef: It's already on the way. It's already approved.

Hazel: To already get somewhat of a test for tinnitus?

Josef: Yeah. So before they can do that, they will have to go through all the approvals, of course, to include tinnitus patients as well. But I think if we sort of say these are the same patients, but in addition one of their symptoms is tinnitus, I think it should be possible to add that on.

Hazel: That would be really interesting to see, for sure. Yeah. Another avenue of possible treatment that you've talked about in the past is to address **serotonin** depletion because your theory was that this could be a contributing factor or cause, I'm not sure which, of tinnitus. Can you talk a bit about that?

Josef: Yeah. I definitely can't get it out of my mind because I remember that study that I read many years ago at the very beginning when I got interested in tinnitus and sort of was reading up on these things. There was a study, I think it was from San Diego, where they tried serotonin reuptake inhibitors, antidepressants, in people with tinnitus. And the result was, as it seemed, kind of disappointing because there were some people that responded to this therapy and the tinnitus got less, but there was also a group where the tinnitus got worse.

Hazel: Right.

Josef: And another group where nothing changed. So they basically... the study ended up in the garbage bin and people said, well, **serotonin reuptake inhibitors (SSRIs)** don't work. That's sort of the accepted outcome in the field, the tinnitus field, people don't think antidepressants work. But I think, I've talked to psychiatrists who work with depressive patients and they say, well look, it's actually the same thing in our field. Antidepressants work in one third of the patients. They don't work in another third, and in one third it actually gets worse. So it's exactly the same outcome.

Hazel: That's true and that's funny it's also what we...

Josef: But it's an accepted treatment. This is the main form of treatment of depression and we don't accept it. This is ridiculous.

Hazel: And we've seen that, by the way, in basically all the clinical trials that have ever been done for tinnitus as well. There's never been any treatment that gives a better result than the one third, one third, one third. Roughly...

Josef: That's exactly right and that's very typical and I think we have to reopen the issue and then work with the third where it actually works. There are subtypes of tinnitus. That's another thing that's become clear in the last few years, and it's probably even mentioned in that big paper with the many authors, that there is diversity and there's different causes even and they cause different types of tinnitus and they probably respond to different treatments.

Hazel: Yeah.

Josef: So why not reopen the issue? And I definitely have plans to do that, but then there's a funding mechanism out there where they welcome sort of new uses of old medicines basically. And I think that under that umbrella, I think we can try this again.

Hazel: Yeah.

Josef: Because the problem is always, you need funding for all the things you do.

Hazel: Yeah, and developing something new from scratch is so time consuming and expensive. Why not just test existing medications and treatments for tinnitus?

Josef: Yeah. Off label use is very common in medicine. And sometimes, you get surprisingly positive results out of these studies. So that's the plan with the serotonin.

Hazel: Yeah.

27:08 Lidocaine cures tinnitus?

Josef: And then we have another study plan that maybe I've been talking about the last time we met, is actually also to go after these transmitters, which ultimately are what we need to understand. In that case, it's **dopamine** that we are trying to study. This is in a collaboration with the **Technical University in Munich**, which is also our partner institution for the **Neuro-engineering Center**. They have one of the few institutions in the world that have a PET/MRI scanner. We don't have one here at Georgetown and people have PET/CT scanners, but the CT scanner doesn't have the same resolution as the MRIs have. So the PET/MRI scanner that is now available is superior to that. And we are working on a grant. You know, again, you need the funds for it to look at the effects of **lidocaine**. And I'm not sure whether this is something we have discussed before.

Hazel: I've heard about this before.

Josef: It's long been known that intravenously injected lidocaine gets rid of the tinnitus sensation in 70% of the patients. So not all of them, but 70% respond positively.

Hazel: Temporarily though?

Josef: Yeah. It only lasts for a few days, hours even sometimes. But I've seen that happen in myself.

Hazel: Have you tried it?

Josef: I had, yeah. It wasn't intentional. I had to get an endoscopy and woke up from the endoscopy and my tinnitus was gone. And so I said to myself, oh my God, I've discovered a cure for tinnitus. And then unfortunately it came back after a couple of hours. But still I sort of went back to the anesthesiologist who did the anesthesia and he said, well, you take **propofol** and anesthesia for all endoscopies all over the world. Propofol is now the medication of choice, but propofol has the downside that it can cause enormous pain in the veins. There are pain receptors in the veins. So in order to counteract the pain, we give **lidocaine**. And there's no danger. This is sort of unproblematic and we add a little bit of lidocaine and then they have no pain.

Josef: And this is how, I don't know whether this is how it was discovered, but it was 50 years ago at least, there was a wave of these studies for a while for treatment, but then because it doesn't last very long, people gave up on it. But I think it's an incredibly interesting mechanism that one has to pursue and find out what causes this effect. And then maybe we can work on prolonging the effect and maybe find other drugs that sort of have the same effect, but where it lasts longer. So this is what we're doing in Munich now. And hopefully, we'll get some results and I can tell you about them in our next interview.

Hazel: Yes, that would be nice.

30:18 New funding opportunities through aging & chronic pain

Hazel: So you did mention a few times we're trying to get funding for this or for that. We also had the experience when we did the podcast, I think you were trying to fundraise, I think, $50,000 or so

through crowdfunding and that turned out to be extremely difficult, which we were not too surprised by. I think you raised maybe something like $10,000, which I think a lot of that came through the podcast actually, so I'm happy that we were able to contribute in that sense. But yeah, it just demonstrated once again how difficult it is to raise funding for tinnitus, whether it's through the general public, like the example I mentioned, or through getting grants, which you're trying to do. Has anything sort of shifted in the past few years? Are you more optimistic now?

Josef: Well, I mean, there is a lot of fundraising for aging studies. Most of the rich people are getting older and, so there are, especially in the United States, there are some incredibly rich individuals and they are also sometimes very willing to support research and we are very grateful for that. And so our fundraising campaign has just started for a new center and tinnitus is actually at the core of this fundraising. So we hope that we will be successful. And, tinnitus is definitely an aging problem as well. If you look at the numbers, sort of in the textbooks you read 10 to 15% of people have tinnitus, but if you look at age, older people, age 65 and older, this number goes up to 45%, you know? So it's actually wrong to cite the 10%. It sort of belittles the disorder in terms of numbers. If you take the older segment of the population, it's almost half of the people that have it. So if they get bothered by their tinnitus, they should try to do something about it and support research on tinnitus.

Josef: So we're hoping to convince people that this is worthwhile to... And I think it's also a disorder that is not just... it is more than just the tinnitus. There's other, sort of very pervasive disorders that fall on the same rubric of gating mechanisms that are no longer working. Chronic pain, for example, is incredibly pervasive. And it's just been at **NIH**, there are different institutes. I don't know, this may not sound relevant, but it is for the funding issue. There is the **NIDCD**, the **Deafness Institute**, that is asked and is supposed to fund most of the tinnitus work, but they're a very small institute. Whereas pain studies are supported by the **Neurological Institute**, and they're one of the biggest institutes of NIH. So if one could get those guys interested in it, I think we would be able to maybe raise more funds. There's also, if one buys into the idea that there's a mood disorder behind some of these tinnitus cases, one could get the **National Institute of Mental Health** interested. This is the second largest. But whenever I go there, they say, well, this is a deafness issue.

Hazel: Right, you talked about that before. They say, oh, no, it's hearing.

Josef: Yeah.

Hazel: But it's not just hearing. It's very multi-disciplinary...

Josef: And so it's a very bureaucratic obstacle that one is sometimes facing, who can fund and who cannot fund these kinds of studies. So I think we have to become more savvy in terms of making our argument and say, well, it is mostly not in the ear. We know that, but it is a hearing disorder. But it also has other aspects that could be transferred towards other disorders. And so we'll see. I think it's very important, the work that you do in talking about this disorder and making it more widely known. I think it's very important.