

TINNITUS TALK

— PODCAST —

EPISODE 13



## TINNITUS AND THE POWER OF PREDICTION Dr. Will Sedley

00:00 Introducing Dr Will Sedley

**Will Sedley:** “The thing I do occasionally take a bit of issue with is the argument that the treatments are there already and the reason they’re not working is because of subtypes — that actually if we just matched our existing treatments correctly to the right people, then everyone or lots of people could be cured. A response I give to that is: show me the one person you cured and then we’ll deal with why we’re not curing everybody.

**Hazel:** Hi, everyone. Welcome to the **Tinnitus Talk Podcast**. I’m very happy to be here today with **Will Sedley**. Will is a researcher at **Newcastle University** in the **UK** and also a clinician in the field of neurology. Am I saying that correctly, Will?

**Will:** You are, yes. Thanks Hazel. It’s great to be here.

**Hazel:** Great to have you on. So, can you maybe just start by telling our audience a bit about your background and what it is you do?

**Will:** Yes, so I am a medical graduate and I spend at least half of my working life working in a neurology department, that’s running clinics and dealing with emergencies and referrals on the wards. Then I’ve been fortunate enough to be able to be conducting research in areas of my interest in parallel with my clinical training ever since I got out of medical school, so I’ve been very interested really in how the brain works and what goes on in the brain to shape our experience of ourselves and the world, which is what has brought me to tinnitus, which I have been working on for over ten years now and has remained an enduring interest of mine.

**Hazel:** And can you tell us how that interest first got sparked? Because, I imagine something must have happened that made you think that tinnitus might be an interesting or worthwhile subject to study?

**Will:** It's a good question and I'll be totally honest because I think this is relevant. At that point where I realised that yes, tinnitus is a really interesting thing to study came considerably after I first made the decision to start working on tinnitus, which really was pure accident. It's something my research supervisor suggested. I'd been working on very basic science processes, by which I mean trying to understand normal functioning of the brain but without there being a direct applicability to people or patient groups struggling with any particular symptoms, and he'd suggested working on tinnitus and within a little while of beginning that, I think I began to realise that, actually – I mean I'd always known this was an important problem experienced by many and not adequately solved, you know not by a long shot. What it took me longer to realise, although not that long, was that to really understand tinnitus you've got to understand every level of the sensory and perceptual pathways, you know right down from the hair cells in the ear that turn sound energy into electrical energy, right up to the brain's higher perceptual network and generic but very complex mechanisms for how we really make sense of the world around us and react to things.

**Hazel:** Alright, so if I understand correctly, you kind of just happened on the topic and as you were studying it, got more and more intrigued by it?

**Will:** Yes, we started out by testing some really simple hypotheses that had been around at the time saying, "oh well tinnitus is just directly correlated to this or that one particular process in the brain and that's that, and all you have to worry about is how that process is generated," and I started out trying to replicate or support some of these theories and found that actually the results that I was getting were really surprising and a much more complex pattern that could not be so easily explained, and so I really just started grappling with just how everything could be put together for a number of years really. And keeping on returning to it in light of the things we were still learning about the condition, and about neuroscience in general. Just in terms of how to explain things because it's funny, you enter a field of research and you just assume that so much is known and what's been written is all correct. Then the more you get into it you realise the less is known confidently and the more questions are raised and that more questions than answers are often raised. So it was an illuminating experience entering this field.

**Hazel:** Yes, that's interesting and I guess it applies probably to a lot of fields but maybe particularly tinnitus because it's still very, very young, right? It's not that long ago that people started seriously looking into it.

**Will:** I think you're right there. I think it is a young field and we may return to arguments as to whether it's generated the interest it deserves, given its scale and impact. So, it's a young field. It's maybe not much over two decades that serious attempts to pin down the neuroscience of tinnitus have been made and it's even towards the latter half there's been that real exponential expansion in the number of studies done. But I don't think it's just that. I think it's an inherently an extremely difficult thing to study because it is a very subjective, personal experience and I think of huge parts of it as actually just being that we're checking

that we're measuring the right thing—that what we're measuring really is correlated to that experience of tinnitus and not so many of the other factors that surround it. Whether that's the hearing loss that pre-disposes you to it, the alterations in attention that follow and the hyperacusis that very often, but not always, goes with it. So, it has been increasingly recognised recently, that it's extremely hard to know, even in human studies where people can tell you very eloquently what they're experiencing, let alone animal studies where they can't tell you anything.

**Hazel:** Yes, exactly. For instance I've only recently understood that when you compare brain imaging pictures of people with tinnitus and without, that a lot of what you're seeing in terms of the big structural differences, is due to hearing loss and not tinnitus per se, and so a lot of the early imaging studies on tinnitus that were done, I think they didn't correct for hearing loss and therefore you can wonder in retrospect how valuable those results were.

**Will:** That's an incredibly important point you've hit upon and you do just have to keep that in mind with every study you read about tinnitus and where there hasn't been control for hearing loss. There is a big question mark. Is it hearing loss, tinnitus, or hyperacusis? Adding to the point that there was a review paper by **Jos Eggermont** who is a huge figure in the field with almost exactly that title, focussing on animal research of tinnitus and what we were really measuring. But it is surprisingly difficult to control for hearing loss. One approach that has been taken for instance is a study of entirely people with or without tinnitus with 'normal hearing'. The trouble is we know that the pure tone audiogram, which is the standard clinical measure of hearing, is not that sensitive to the various forms of hearing loss that exist. It really just looks at one type of hair cell function, and you can have really quite significant impairments and noise damage that has accumulated over time that isn't measured by this. Where you can have measurable deficits then they are just very narrow. They slip between the frequencies of the audiogram or they are higher frequency than the normal audiogram goes to and, again, you can just end up measuring correlates of these subtle, subtle changes in hearing unless you are very, very careful.

## 08:10 Early theories and discoveries in the field of tinnitus research

**Hazel:** Can you tell us a bit more about some of those early theories when you came into the field that later turned out to be false or just much more complex than was initially thought?

**Will:** I'm not sure I've come across a single theory that I would claim to be false or such but as you say I think still an open question or not the whole answer. I mean one interesting thing was there has been this big ear-or-brain question and way back people assumed that because you heard the sound in the ear, tinnitus was coming from the ear. There were a number of attempts made to try and cure tinnitus by severing the auditory nerve surgically that connects the ear to the brain, and the fact that that very often made tinnitus worse was one of the very strong initial pieces of evidence for why tinnitus is generally now understood as a brain condition. If it was just as simple as cutting off this firing that was being passed through to the brain from the ear that should get rid of it, but it often made it worse and that is what led to this idea that the ear's role in tinnitus was to have reduced input coming in and that the brain somehow did something a bit like phantom limb pain to over-compensate for that. But

actually, it's still not that simple because then what got glossed over was the fact that some people's tinnitus improved after cutting the auditory nerve.

**Hazel:** Yes, I recall that being the case.

**Will:** So not so straightforward and maybe some inter-individual differences there. And some interesting work that came out after I'd started in the field, guinea pigs showing that you can give medication that only acts on the cochlea in the ear and has no action on the brain and that if you give that very early after causing tinnitus in animals, it looks like you may be able to get rid of the tinnitus just in those initial weeks but there may be a critical period where that's the case, after which the brain may take over although some of the work to fill in and do those further studies hasn't been done. But that's the suggestion left by it.

In terms of other popular theories, there's a very popular theory called **thalamocortical dysrhythmia** which was popular when I started, which remains popular, albeit with some refinements and what that said is that if you take away some of the normal input to the thalamus which is the main deep down relay station for sensory and other pathways, so that gets a lot of input coming up from the ear. If you take some of that input away it goes from what they call an alpha rhythm which is 8-12 cycles of activity per second or less to a slower rhythm of more like 4-6 cycles per second and that then projects up to the auditory cortex, the sort of higher hearing centres and entrains it in part of it that's lost its input into this abnormal rhythm, and the idea was that the interface between the normal bit and the abnormal bit gave you these very fast what we call gamma oscillations, which are kind of 40 plus cycles per second and it was the gamma oscillations themselves that triggered this perception and that's what I set out trying to test.

As you say, with many studies there weren't always the best controls for hearing loss or age or other factors, attention and things, which can all influence these things and the approach I took was one that wasn't new but it was new in this context with these measurements which was to use residual inhibition where you play a loud masking sound and once you stop it the tinnitus takes a while to recover. The theory was that if this is true and these gamma oscillations are the basis of tinnitus then when you suppress tinnitus with residual inhibition then the gamma oscillations should go down and return to normal as the tinnitus does and we did see this in some individuals. So far, no surprises.

The real surprise, and by far the stronger finding was we had a smaller group of people in whom their tinnitus got temporarily louder after the masking sound which is what I called a 'residual excitation' but there is otherwise no proper term for it that I know. Again, if these gamma oscillations were the basis for tinnitus then when the tinnitus got louder after the acoustic stimulus the gamma oscillations should go up, but the weird thing was they went down. They showed absolutely the opposite trend, and this was consistent across every individual who showed this phenomenon at both the individual and a group level. That I found extremely difficult to reconcile with the contemporary theory and it took me a long time to come up with what I thought was an adequate explanation for the findings but I may refrain from going on too much about that.

## 13:06 Gamma oscillation anomalies

**Hazel:** We can briefly get into that. What was your explanation?

**Will:** I spent a number of years going over it and eventually, at the end of my PhD I just wanted to put all the facts, everything I thought I knew or didn't know or may know about tinnitus in one place. Just put it all there, draw it in together and just think, well how do all these different bits and different levels and the auditory pathway and everything all fit together? What is this really telling us? And part of what came out of that was the idea that there was a fairly newly emerged view, I mean it's very well-established now, not just looking at tinnitus but in general, these gamma oscillations, what they are indicating is prediction errors. To explain what that means, we have to first accept – which is fairly widely accepted now – that the way perception works is that we make a model of the world whether that's the different bits we hear or we see or what is going on in the environment around us, and we update and maintain that model all the time and that model or those models make predictions about what we are expecting our senses to tell us. Much more efficient than just waiting for our senses to keep on telling us every phrase, so to speak. And then when our senses do pass the information on those are compared against what the senses are telling us, compared against the predictions we have already generated and that is used to update the predictions and to influence what we actually perceive and one part of that, the prediction error, is the mismatch between what we expected, based on our models and what our senses actually told us.

The view was that **gamma oscillations are indicating prediction error** and once we accept that, it frees things up a lot because it means they don't have to simply correlate positively or correlate negatively with tinnitus or be the cause. They are simply a signature that what the signal being passed on from the ear is to some extent not matching with the signal, or with the expectation of the hearing part of the brain of what it thinks the meaningful real sounds in the environment are and that led to this idea that actually perhaps the biggest difference between, or what really fundamentally separated people with tinnitus from people equally predisposed with the same hearing loss who didn't have it, is whether their brain changed the predictions of what they were hearing, to expect a constant sound and the reason they changed that is that you've got this noisy signal coming up from the ear which everybody has but when you've got hearing loss that's amplified. Then it's down to the higher levels in the brain as to whether they accept this as a real sound and that helps them get rid of those prediction errors by accepting it as real but in doing so accepting something that, on another level, isn't real, and all the consequences of that or whether to keep on having these prediction errors and keep fighting it, so to speak. And that, depending on certain factors the brain can go one way or another. That's what led to this idea anyway.

## 16:12 Will's tinnitus model

**Hazel:** I guess this is a nice segue into you explaining your view/theory/model of how tinnitus is generated. I think you were already on the way to explaining how you see this.

**Will:** Absolutely, yes. To take a step back, because I realise that I launched straight into the thick of it: What's been thought of as the basis of tinnitus for a long time and for which I can

take no credit is that firstly every pathway in the brain has spontaneous firing of brain cells, spontaneous activity. It's just a thing they do, and the auditory system is no different. If you want an analogy here, for the visual system that's a bit more familiar to everybody whether or not they get tinnitus. If you go and stand somewhere completely pitch dark, you know, there is not a single photon of light in the environment and you concentrate on what you can see, you will see phosphenes. As in little flashing, dancing, random blobs, colours and things like that. And what that is, it is not a hallucination. That is spontaneous cell firing from the retina being passed on upwards. And the auditory system is no different and in fact there is some good evidence showing that, even if you take people who have no awareness of having tinnitus or having ever had it for more than seconds at a time now and then, as everybody does, you put them in a soundproof room with no sound around and get them to concentrate on what they can hear, more than half will report hearing some high pitched sounds, either a pure tone or a narrow band noise, you know like any of us who get tinnitus are familiar with, but quieter and only there in very quiet conditions. So, in a sense that spontaneous cell firing in the cochlea or the auditory nerve pathway, it's there for everybody.

**Hazel:** It's normal.

**Will:** It's normal, so to an extent we have to see tinnitus as the norm. What's abnormal is when it gets particularly prominent and starts to declare itself and to detract from other things even in the presence of everyday sounds and background noise, so it's the extent, not the presence per se.

**Hazel:** Could we say that for people who don't have tinnitus, that the spontaneous firing from nerves in the auditory pathway is somehow filtered out of the conscious experience?

**Will:** I think that is exactly it. So, at some point the brain has to decide what to do with this information, with this cell firing and there are two ways this can go. It can accept it as a real perceptual entity, as a real thing in the environment, a real sound in this case or it can ignore it as noise. And noise as in random activity that doesn't carry a meaning in the information theory sense, and if it ignores it as noise all it goes on and perceives is either silence if there is nothing else going on or whatever other sounds are going on in the environment. So, what we would argue is actually that the signal, it's what I would call the 'tinnitus precursor' this random firing, is there in everybody and normally it is ignored as noise because it is random. It doesn't correlate with anything else. There is no prior experience of it. There's a large number of cues inherent in it that tell the brain it's not important.

**Hazel:** So, to clarify, when you say 'ignore' you don't mean consciously ignore, but this happens at... you just mean at a subconscious, involuntary level?

**Will:** Absolutely, all of this taking place before anything reaches conscious attention, so conscious ignoring is more like habituation, which is a whole other matter. We might draw parallels, but it is largely separate.

In terms of things which predispose people to tinnitus, again this is nothing I can take credit for, but if you damage the input to certain nerve pathways from the ear, by damaging the ear or the auditory nerve then through homeostasis the cells that are fed by those, they like to

maintain the same overall firing rate. That's how much they fire in response to sounds they hear and spontaneous firing rate. And because they've been deprived of a lot of their input that sort of response gain or volume is turned up to preserve the same firing rate and what happens is most of that becomes spontaneous firing now and that's well documented. If you damage someone's hearing, a human or an animal spontaneous firing rates go up significantly and, not only that, but how synchronous the firing is across different nerve cells again goes up and that's important. If you have a lot of nerve cells all saying the same thing at the same time, they're much more impactful and are much more likely to affect ongoing brain processes than if they all, say, fire and say things at different times.

So again, that is how someone is predisposed. But you can have two people with the same hearing loss, one of whom gets tinnitus and one of whom doesn't. And what I've argued is the key step, it's this. It's whether it gets accepted as a sound source and therefore a model and a prediction and everything corresponding to it is set up which suddenly correspond with the activity and then the whole system makes sense and you perceive it. Or whether that part of the system continues to ignore it as noise. So it's not just the hearing loss in that activity itself but it's these other factors and I've come up with a list of a number of things that might influence this and a term we use is 'precision' which is the brain's estimate of how important or reliable the source of information like this tinnitus precursor spontaneous firing signal is, and that is influenced by things like chemical factors, sleep deprivation, stress levels, attention plays a big part, so focussing attention in many views of brain function focussing attention on a particular sensation is exactly the same as increasing the precision on it. So there can be a whole host of single or interacting factors that are changing all the time and depend on your individual state, where you're focussing your attention, other things that are going on and that what needs to happen for tinnitus to occur I think, is that together these give that tinnitus precursor signal enough precision that it gets brought over that threshold, where it gets accepted as a real sound source, a real sound entity and you hear it.

And after that, it's only a matter of time before that learning of it, that acceptance, that forming a model and a prediction to go with it becomes persistent. Once you've recognised it once, it's very hard to 'unlearn' something, to forget it, or to no longer recognise it. The example I use – I know this is a Podcast so we can't quite illustrate it – but there's a very famous picture which is a load of black dots on a white background and they just look like random dots at first but if you look at it for long enough you realise at some point it's a Dalmation dog sniffing at the base of a tree. And once you've seen it, that pattern in it, you can't get rid of that. It doesn't matter how many years go by and you see that picture again you will see it straight away. And I think it's something similar with tinnitus. Once you've seen the pattern and the meaning, again, totally subconsciously before anything you have any choice over kicks in, once you've seen that meaning and a pattern in the random firing then you can't really shake it unless you get rid of the random firing or suppress it enough that it goes back below the threshold. Or you have enough competing noises or sound sources or unless you were able to find a way to see how that learning process was actually maintained in the brain which would be a very subtle thing that's to do with particular connections between multiple centres, and disrupt that. So, actually getting rid of tinnitus, once it's established, it's not to say it's impossible but it's a huge challenge.

**Hazel:** Yes, I think we want to get back to that later, for sure. But to maybe make an attempt to crudely summarise your model, can we say that someone with chronic tinnitus, their brain has learned to predict the tinnitus signal and because there is this prediction or expectation to hear this tinnitus that is why you continue to hear it?

**Will:** Yes, I think absolutely the prediction and the expectation is there and there's still the spontaneous firing in the auditory pathway that corresponds to it so it's enough, the prediction to keep hearing it and that activity is enough to keep reinforcing it or not challenge the prediction.

## 25:25 Factors that trigger tinnitus onset

**Hazel:** You have talked a little bit already about how there are many factors that could go into triggering this kind of prediction. Can you talk a bit more about that and can you also explain whether you are saying that the brain of someone with tinnitus is innately predisposed to having this prediction or is it more like environmental factors, changes, that cause the brain to start to predict the tinnitus signal?

**Will:** True, it's a good point and I think there are two things here and what I'm arguing is the initiating event is getting the precision of this spontaneous firing in the auditory pathway to tinnitus precursor. It's getting the precision high enough to get it noticed and then there's sort of accepting it as a default state, a default prediction so there may be different factors that influence the two things. And I wasn't initially making any claims about genetic traits although it would always kind of surprise me if there were no genetic and individual traits as individual genetics affect so much but I would say on an aside that, more recently, there has been some very nice work in the genetics of tinnitus coming out and there does seem to be, not that it's a sort of hereditary condition, but there does seem to be a significant genetic element in that if you have family members with tinnitus, you are more likely to develop it. It's always a little hard to tell and see through how much of that is explained through genetic susceptibility to hearing loss versus other factors but there does seem to be a significant genetic component.

Given that a lot of the factors that I think will determine when and whether you get tinnitus relate to your particular state of mind and physiology at the time, I think there's likely to be genetic and personal elements to this and then a large part being particular circumstances just at the time on the day, but these may fluctuate a lot from time to time. And you only have to be unlucky and get over that threshold once for long enough for the tinnitus to be learnt but anecdotally, people, I mean you may get tinnitus at the same time as the hearing loss was caused but the usual scenario is it's a gradual onset hearing loss and then people will say either that the tinnitus came out of the blue or it appeared during a time of great stress or difficulty or when physical illness was happening. Sometimes it's other things. Very innocuous things. I saw somebody who had a hearing test, just a routine screening hearing test and that involved having to listen out for very quiet sounds in a very quiet environment and the tinnitus just emerged during that and never went away again. I don't know whether you've got people who report similar things?



**Hazel:** No, that seems quite a rare case but on the other hand It doesn't entirely surprise me, and it does seem to fit with your model, for sure.

## 28:36 Fundamental differences in auditory predictions – people with and without tinnitus

**Will:** On the subject of whether people with tinnitus have fundamental differences in the way in which they form auditory predictions there is some interesting work starting to come out about this. I've got some colleagues based in Salzburg, who've looked at the auditory predictions in people with tinnitus and people without and these are very low frequency sounds in the range of normal hearing, well away from the tinnitus and it's a sort of complex pattern of different pure tones and there are different structures and rules about how they are related to each other, such that it lends itself very well to people needing to form predictions in order to best predict and anticipate what's coming up. So naturally people will do that and then by looking at the exact brain responses you can see which frequency of sound is being represented or even predicted at any one moment in time and the people with tinnitus, if anything, seemed to actually show a stronger or more accurate pattern of brain responses in terms of predicting what is generally likely to be the next upcoming sound so they were more likely to have started representing the correct upcoming sound before it even started playing or at the time it started playing, but too soon for the response to that sound to have occurred. They were anticipating it better in advance than people without tinnitus. So, you could turn things on their head and given that we've all got this sound source there is the anomaly, is the worst performing brain the one that doesn't find the tinnitus and doesn't find the pattern there?

**Hazel:** That's an interesting way of looking at it. So, the brain of people without tinnitus are worse at predicting sounds. I guess it's not necessarily an advantage that you'd want to have as a person with tinnitus, but it's an interesting way of looking at it.

**Will:** No, I think there are few people who would want their tinnitus, if given the choice. I think the best-case scenario is something approaching an indifference. But, yes, these are new, preliminary findings from a single study, so I mention this as something people are beginning to look at, rather than us being able to draw any firm conclusions. But you know I think things like this when we are dealing with conditions that are so common, we do need to try and ask ourselves, actually is the condition itself of an evolutionary advantage or does the condition arise from other traits that present an evolutionary advantage so you know there may turn out to be something to this.

**Hazel:** That's a very interesting question and I hadn't considered it before but I could imagine you know when we were all living in caves in the stone age and if you are very attuned to environmental sounds and picked them up more quickly or were also more attuned to changes, if a sound is there and it goes away or the other way round, that could be an evolutionary advantage in terms of waking up in time when a predator comes close or things like that.

**Will:** It's a good point and makes a lot of sense and has a lot of face validity. I'd need to check and couldn't tell you whether any such factors have been explored for in tinnitus. I think it's

always difficult once the tinnitus has formed to know what are the predisposing traits versus a reaction or in some way a downstream consequence of the tinnitus, but I like that thought and that would concord with the way in which I've been maybe starting to see things.

### 32:31 Tinnitus causes

**Hazel:** So it seems like whatever it is that sets off the tinnitus it's got to be quite a complex interrelation of different factors including spontaneous firing in nerve cells and then potentially some kind of genetic predisposition, and then whatever environmental factors come in, in terms of injury or disease or stress. Those kinds of things. I think if that's the case, because I think a lot of people when they get tinnitus, they start Googling causes of tinnitus. And you find these lists online of causes. It's a long list including things like certain medications, head and neck injuries, Menière's disease, acoustic trauma, emotional stress, temporomandibular joint disorder. But really, we've got to say it's much more complicated than that and those things might be triggers but not causes, per se. Would you agree with that assessment?

**Will:** Yes, I think we should maybe draw a distinction between causes and mechanisms because causes are what we'd think about in a medical or clinical setting which are the things that put you at risk, you know you know they are tangible things, and they are mechanisms for what is actually happening in the brain. I think the mechanisms are inevitably complex but I think we can take a big step back and zoom out and reduce tinnitus down to a small number of simple elements and I think what we'd say is tinnitus is your brain picking up on random cell firing in your auditory pathway as if it were a source of sound. Why this happens is either that there's some combination of that random firing getting amplified and becoming very loud or the brain tuning into it more, or both.

Risk factors-wise, I tell people all you need to develop tinnitus is generally some amount of hearing loss which can be anywhere from mild or undetectable upwards and all these other causes, in my mind, are just things that cause hearing loss and, yes, they're all worth considering but it's almost never the case that any of them are there. Tinnitus is a tendency to hear random cell firing in the auditory pathway as if it were real. Risk factors are hearing loss and anything that causes it and how it happens is some combination of amplification of that activity and changes in the brain's vigilance or the way it picks up on it. It's a condition or state, not a disease as such, which doesn't detract from its impact in any way. And the only thing I'd add on top of that which I think it's relevant to pick up on aside from considering reversible causes of hearing loss, is whether there are any pointers towards somatic hearing loss such as TMJ or, more commonly, the cervical extensor muscles at the base of your neck, just because there's some evidence that those can respond to successfully targeting those sources of muscle tension which may be around 20% of cases. But, other than that, it's deal with hearing and then manage tinnitus in one of the standard repertoires of ways for managing tinnitus which we may come on to, and I realise are not satisfactory for most.

**Hazel:** I think that's a very nice summary of your model.

### 36:13 Other tinnitus models and how they compare

**Hazel:** Could you talk a little bit about other models out there and are they very different to your model and are these different models mutually exclusive or could they somehow all be true? So, could you talk a little bit about the other models?

**Will:** Absolutely, and I don't think they are mutually exclusive, and I think they are complementary, so I think it could be that multiple ones of these are true and are each part of the story or some apply more than others in other cases. What I was trying to do is come up with a framework as such by which they can all work together and not be contradictory towards each other. It's fairly straightforward. I tend to see things in quite simplistic terms. You either have something causing excess activity in the ear or the auditory periphery sending signals through that would be peripheral tinnitus. The next model is the ear's role is to be underactive, send too little input and therefore the gain is turned up in the central pathway and it's just overactive. The central gain models.

There is a popular model about '**frontostriatal gating**' whereby there's a noise cancelling where there is a system that involves parts of the pre-frontal cortex and basal ganglia and this feeds back into deep pathways in the ascending hearing pathway and that has a gating role in determining what gets tuned down or filtered out and what gets tuned up. So, you know where that fits in if that is the case, that's another gain model because ultimately all that's doing is turning up or down what finally gets through to auditory cortex. And then you decide, do we think that's enough if a certain amount of input gets to auditory cortex, will you hear tinnitus? Which I've argued I don't think it's enough to explain things, in which case you need another mechanism such as this prediction-based model whereby how is that actually processed, interpreted and incorporated into perception and this involves some wider brain networks.

And the only other real remaining model I am aware of is then a sort of 'filling in' model, or the phantom limb type model where you say, well, actually a part of the auditory cortex has lost its input, that it's just not getting it from the ear and that what it's doing is therefore what it's doing is it has to get it from somewhere else which is either pull it in from neighbouring parts of the auditory cortex from frequencies that haven't been damaged, or damaged so much, or pull it in from memory if the hearing is so bad that it's pulled in memory. Those models I think are difficult. I think that's the only one that doesn't fit really neatly with the account I've put forward. It is a bit of an alternative and then you have to say well, which is it? Is there too much activity, too much gain and therefore too much comes from the auditory periphery and from the ascending pathway and reaches the auditory cortex or is there not enough reaching the auditory cortex and it has to pull it in in a top down manner from somewhere else and you can come up with nuanced ways in which they can work together.

The other popular model I mentioned is '**thalamocortical dysrhythmia**' which, again, says that the thalamus, the auditory hearing thalamus below the level of cortex isn't getting input and therefore it goes into this mode where it changes its frequency and paradoxically it gets too little input and that makes it give too much output.

**Hazel:** So that's another variation on central gain?

**Will:** It's another variation on central gain, exactly. I think most of tinnitus comes down to central gain. If your angle is brain chemistry, you know, too many excitatory chemicals and not enough inhibitory chemicals, again, that's gain. If you're interested in synchrony, so how in tune the firing of all your different cells in the auditory pathway across different frequencies are, again, that can be understood as gain because, ultimately, they all pass their messages on to the same targets and if they all fire at the same time that triggers a much stronger response than if they all fired at different times. So, a great deal can come down to gain. And I think it's useful to think of a common currency here. The way I see it, it is gain, but it's something more and it's how that signal is processed, not which is influenced by how much gain there is or how strong it is but also by our predictive mechanisms, by precision and how tuned into how receptive we are and how vigilant we are for sort of new or unfamiliar or potentially threatening sensations.

**Hazel:** Is this related to a comment or claim you made in your 2016 publication entitled '**An Integrative Tinnitus Model Based on Sensory Precision**' where you say something like "all the other models face a paradox"?

**Will:** It is sort of, yes. It is very much related to that and I think what I was trying to solve were two issues with that paper. One of which was that some of the models seemed contradictory to each other and I was trying to explore whether we could put them into a framework by which they were no longer contradictory but complementary or, at least, non-mutually exclusive alternatives and then the other things I highlighted were these paradoxes. For instance, if you were to take central gain as a model, that actually hearing loss seems to be the main thing that changes central gain more so than tinnitus. It's actually not that clear whether tinnitus explains it any more as central gain once you've fully taken into account hearing loss and hyperacusis. And given that that would have occurred at the time the hearing loss occurred and then you get massive changes due to hearing loss and comparatively smaller changes, if they do occur at all due to tinnitus, well how does that really present the whole explanation if the level of hearing loss is not the predictor of tinnitus? If the timing of the hearing loss is not the predictor of tinnitus. If actually you can go on to develop the tinnitus much later then again there's something unsolved and unexplained here. I

think the other paradox is one I've mentioned before with these very high frequency fast gamma oscillations that they seem to have different relationships with tinnitus in different settings depending on how tinnitus changed and again, it's not really telling you the whole story. They are part of the story. I think it was highlighting things like that that just showed the incompleteness of the existing models.

### 43:11 Can any of these theories be proven?

**Hazel:** So, one of our **Tinnitus Talk** members submitted a question which has also occurred to me, whether any of these models can be really proven to be true with the current brain investigation tools that we have at our disposal such as MRI and ABR, etc?

**Will:** It's a really good question because each of these gives you some sort of indirect measure of brain activity, and then the measurable brain activity gives you part of the story of what is actually going on underneath. I sometimes liken this to — we are trying to judge or prove or

measure the content or meaning of a conversation by listening from a few miles away. But it is simply just measuring the volume of the conversation and it's an extremely interactive measure, so what you end up having to do is construct theories or models of what you think may be going on underneath and then use that to sort of model what you would anticipate — your things like the volume of conversation or things you can measure — the brain responses we can see — under different conditions and see if it all matches up, and obviously if the arguments or models are relatively weaker, we just take all the existing data we have and say, well, what is the best explanation or the least worst explanation for it. And a bit stronger if we can go, yes, based on that model, if we run this or that new experiment then this is what we expect to find. That's a bit stronger if you then confirm that hypothesis.

If you can truly sort of understand a system in mathematical terms — in computational terms — you can build a computational model, a computerized model, and see if you can use that to sort of fully explain perceptual tinnitus behaviour in animals under different conditions, and that's been done for certain levels of the auditory pathway which are quite well understood. They're just not quite there for the more complex systems involving higher brain centres as well. So, I've been trying to do a sort of 'middle ground' thing for now, which is the second scenario, saying well, if this is our theory, what else would we expect to find if we run these new experiments, and I've been running some of these new experiments and so far coming up with more or less what we would expect to see given the model I'd come up, albeit, there are always going to be other potential explanations so that's something we have to continue working at, but the short answer is that it can be done but it is very difficult to really prove how something is working when it is a subjective perceptual entity that is an emergent property of these very wide, very detailed brain networks. It's not impossible. It's just a massive, massive, challenge.

## 46:16 Current research and plans

**Hazel:** Maybe this is a good transition for you to talk about your current research or your plans and what is it you would most like to find out going forward. I imagine you want to prove your theory to a greater degree of certainty?

**Will:** Yes, if it's correct. I want to help to discover what's going on. Whatever that is — whether it concords with existing theory, my own or others, or if it's something totally different. The preferable answer is the correct one. But, yeah, I'd like to understand tinnitus better and get at what's going on.

**Hazel:** That's a good point in science. I guess disproving a theory has as much value as proving it.

**Will:** Um, yes. There is. There's a time to knock things down when they're a bit too established and there's a time to build when you're left saying "where do we go from here?" and to some extent it's an ongoing cycle of breaking and rebuilding. I'd love to make headway with what's going on and I would love to help work towards better treatments for tinnitus.

**Hazel:** So, barring any sort of practical or financial constraints, what would you most like to research in the coming years?

**Will:** I'm really interested in tinnitus and related conditions where there are ongoing, unpleasant, perceptual, unwanted experiences, which include tinnitus and also chronic pain and some other conditions like fibromyalgia and disturbances of sensory processing of which pain can be a part even in the absence of tissue damage, and I think there's a lot of parallels. So I think with all of these and tinnitus as much as ever, in an ongoing fashion I'd like to nail down what it is that is controlling the extent to which sensations are tuned up, tuned down, allowed to reach conscious level or not, in a way that opens the door to being able to modify that, and tune things down that are too intense or too loud, like hyperacusis, or turn the switch back on things that are there that shouldn't be like tinnitus or ongoing pain and I think there are a lot of parallels across the different fields because fundamentally the brain isn't going to have totally different tools redesigned from the ground up from one modality like bodily touch sensations or another like hearing to another like vision. The commonalities are going to be very large here. So, I'm really kind of looking to try and understand the fundamentals of these systems, but in a very clinically relevant way, never losing the focus on tinnitus here.

**Hazel:** So, you will be studying actually these different conditions that are perhaps analogous to tinnitus such as chronic pain, you mentioned?

**Will:** Yes, the plan is to continue to spearhead things with tinnitus. I think the research is much more established in the methods, so I think that, for the foreseeable future that will remain my primary focus and I'm keen to sort of start to bring what we're learning from this to other conditions subsequently, and I think the study, it's one of these things where actually you can often make less progress by focussing too narrowly on one thing as opposed to considering the bigger picture when you're dealing with things that are so similar.

## 50:02 Finding an objective tinnitus marker

**Hazel:** So, a few months ago you shared with the **Tinnitus Talk community**, and there's a thread you can find on the Forum for our listeners, you shared with us a research idea, which entails different elements, but amongst those elements is finding or defining an objective marker of tinnitus. So can you talk a bit more about that? What is currently the closest thing we have to an objective measure and why is it so important to have a reliable objective measure of tinnitus?

**Will:** Yeah, it's a good question, and the first thing I'd say is nothing is intended to become a diagnostic test because we're fortunate, you know, anyone working with people with tinnitus have a very reliable measure which is more reliable than any medical test will be, and that is simply asking the person "what are you hearing?" or even just, "do you have tinnitus?" There is, for research points of view, it's useful to have objective measures that are tied to or linked to particular parts of the mechanisms of the condition, so that if you are testing treatments, for instance, you can tell not only that someone says their symptoms are better but also you can see some additional line of evidence that you are modifying the related brain processes—assuming the treatment works on those processes. So that's the sort of desirable thing, it's not essential and you can absolutely get by just asking people if their symptoms are better, and if you conduct your studies properly and have a good placebo group then you will still see

your effects. But nonetheless it has still been a bit of a barrier for the drug companies and enticing them to invest in tinnitus research.

I think the bigger issue is for animal studies. There is so much more we can learn about brain mechanisms. There's things we can do in animal studies — not that I do them myself, but I can recognize their importance in animal studies — that we can't in humans, not ethically not feasibly, and for that it is really important to know is your animal hearing tinnitus or not, because otherwise you may be misled or studying the wrong conditions — studying hearing loss or hyperacusis or other aspects of impaired sound processing that follow what you do to the animals.

There are measures of tinnitus in animals and these are ingenious — brilliant creative minds have gone on into producing these, and by and large they fall into two categories: you either train an animal to do something or not do something, a particular behaviour in the presence of noise, and then you do whatever you think may cause the tinnitus and you see how it behaves, whether it's behaving like there's a noise there or there isn't, or you can look at the startle response, sort of involuntary responses that don't need that prior very laborious training. That's — the main one is this **gap-prepulse inhibition**. So there's something called the **acoustic startle response**. If there is a very loud sound, it's startling, and for rodents they actually visibly twitch and move their ears and things like that, and that can be measured quantitatively. And if you give a warning, an implicit warning that the startling stimulus is about to occur, then there's less of a startle because they are expecting it, and one form that that warning can take is you can play a quiet ongoing narrow band sound of some kind and there can be a short gap in that sound very shortly before the startling stimulus or sound, and that diminishes the startle response because they were expecting it. However, the line of reasoning goes, if you've got tinnitus, it will fill in the gap in that sound so you won't hear the gap and therefore you won't be any less startled than you would have done without gap. And there's way you can compare with gap, without gap different frequencies and things and come up with this index of whether the animal has tinnitus. And there's a number of controversies here and there's also the fact that this is not clearly replicable in humans so there is no validation against any gold standard for any of these measures. You can show that some animals will behave in the manner you think they'll behave if they have tinnitus, and that is more likely to occur after you damage their hearing or over-expose them to noise, but there is no gold standard at which you can go well, actually this is the accuracy, this is not— so at the moment we have this big unknown over how accurate the animal models are; they may be brilliant, they may be very much misleading us and it's very hard to be sure.

So, what I am very interested in is can we come up with an objective marker in humans that then the animal research community could use equally in animals, and if it can be validated, it could be very accurate in humans. They could either use that as a test for tinnitus in animals or even just use it to validate the existing models, whichever proves to be more convenient. Once you have that and you absolutely know which animals are experiencing tinnitus, then actually, the results are — one can put a lot more stock in the accuracy of the results of any of the studies derived from those methods really. So, it is again a bit of a limiting factor on these lines of research and, you know, again, if your measure doesn't actually reflect tinnitus but something else and then you come up with a medication that you give to animals and it normalises it, you may be treating something other than tinnitus and that would be one of

the several possible reasons that treatments that work in animals often don't seem to work in humans. So, it is really important to know, particularly in animals, what it is we're actually studying.

## 55:51 Proposing an objective measure

**Hazel:** So, what objective measure are you proposing, because I think it's related to your prediction model, correct?

**Will:** It is absolutely. Yeah. So the idea is that we can't measure predictions themselves in the brain — these are just at a level of subtlety down to connections between large numbers of cells not any activity we can observe, but what we can make use of is that there are well characterized brain responses — even ones we can measure with EEG, for instance, that indicate the violation of predictions, and the more strongly a prediction has been violated, the bigger this brain response. So, with the right different conditions that you measure in these prediction violations across, you can start to work backwards and say well, actually, it's telling us this or that about the predictions. So, what I'm focusing on is again, my theory that people with tinnitus have an ongoing prediction of a tinnitus-like sound — a quiet ongoing sound at a particular frequency. And the idea was that that prediction may not necessarily only act on the spontaneous firing that causes the tinnitus itself but may act on other sounds of similar frequencies played, and it's quite a simple design, what we've been using.

You just play a series of beeps at a particular frequency that generally louder than the tinnitus, and then every so often they switch and they go louder in intensity, and they play the louder ones for a while, and then every so often there's a switch back to the quieter ones, and it just alternates in intervals between loud and quiet. And every time there's a switch, a so-called deviant response — there's a deviation of the intensity or loudness of the sound — that triggers a large brain response where there's been this perceptual change. What I hypothesized is actually because in one case where the sound's getting louder it's getting less like the tinnitus, and in the other kind of deviant it's getting quieter or more like the tinnitus, we should see an asymmetry here — that the ones getting less like the tinnitus should give you a much bigger mismatch or deviant response because they're more unexpected and the ones that get more like the tinnitus should actually have been much more expected, and so what we expected is very much an asymmetry that sounds a bit louder and give you a much louder response than the ones getting quieter, and this is after correcting for straightforward things like the responses to the different sound loudnesses themselves.

And that's what we've seen in the initial studies, in the first few studies, is encouraging; it seems to support the hypothesis and potentially be a strong enough effect to actually tell you not only that a group of people, but whether an individual, has tinnitus or not. So there's further work ongoing that Kate, my Ph.D. student, is doing to replicate this to refine the methods, try and make the effect as strong as it can, and run some additional controlled experiments to be sure that we are really — the reason for these effects really is for the reason that we think, because obviously as I mentioned, there can be other explanations we haven't thought of.



## 59:10 The accuracy of Will's objective measure

**Hazel:** So what level of accuracy have you been able to achieve in terms of this test being able to determine does someone have tinnitus or not?

**Will:** Yeah, so we look at something called the ROC or Receiver Operator Characteristic curve, which is something you make for any diagnostic test, and it looks at all the different positions you can put your cut-off point, your threshold, for what you say is a positive or negative test. So, at one end, you can set a very low threshold, and so you would detect everybody with tinnitus because they'd all be over that threshold but you'd also detect probably everybody without tinnitus. So that what you'd call a test that — it's sensitive but it's not very specific, so even if you test positive it doesn't mean you have that condition, and at the other end you can set the threshold very high so you detected almost nobody with tinnitus but you were fairly confident that if they tested positive, they were to have it. And you can draw a graph of every different place you can put your cutoff. You can look at the area under the curve of that graph and a perfect test has an area under the curve of 1, meaning it perfectly discriminates everybody, and a useless test is 50%, so it's no better than chance, so it's 0.5 area. We were up to about .74 if I recall correctly, so about halfway in between which is what gets classed as fair diagnostic accuracy, not quite good and not excellent, but still showing some significant value. We'll have to see what that comes out as for the replication study and then with further refinements of the methods. We'll have to wait a little bit longer due to the global pandemic for when we get those next results.

**Hazel:** Of course. Yeah, that's been affecting many researchers. And does a refinement of this objective measure also help you to refine your model of the mechanisms, underlying mechanisms, of tinnitus?

**Will:** I think there's two ways in which we're sort of trying to move things forward. So, there's refining it just to make it — just to give you as clear a result as possible, which would make it a more useful test, but not shed any more light on the basis, the actual mechanisms behind that or previous models. And then the other thing we're looking at doing is slightly changing the methods and exploring slightly different conditions again to just try and approach testing the hypothesis from slightly different angles to additional conditions and relaxing some of the assumptions we've made. So, it's a little bit of both, probably with separate experiments.

## 1:01:53 Sound therapy plans

**Hazel:** I understand you're also working or planning to work on some type of sound therapy. Can you tell us a bit more about that?

**Will:** Yeah, so that's something I hope to start testing fairly soon. It's a little bit more work for the infrastructure to be done. Now there's obviously been a lot of sound therapies tested in tinnitus before, most of which haven't worked and the remainder may work a bit. It's not that clear. There are some that seem to work slightly. One has to bear in mind that when you approach these just from history of how they've gone before, there's a high chance that it

doesn't work. It is taking a new approach. It's not something that's been tested before and it is again focusing on this concept of precision, which is the cue to how relevant or how important that activity in the auditory pathway that gives rise to tinnitus is. And we've said that there's too much synchrony associated with tinnitus and probably hearing loss — the cells are firing in the same rhythms at the same time and that makes their message much more powerful and harder to ignore. You can look at this in two ways: either is breaking up synchrony or I mean to break up or reduce precision, but it's all down to sounds. We've got these sounds of how the different, the relationship between the firing rates will cause in different frequency channels at different times and how these are varied. Again, to try and break up any systematic relationships between them and kind of teach the cells in each frequency channel to be firing at different times and not correlate with each other. So that's the idea of it, and anything else I would say on the subject would probably just be excessive jargon at the moment.

### 1:03:43 Expected outcomes of Will's sound therapy

**Hazel:** What are you hoping for ideally? What would be the ideal outcome of that therapy?

**Will:** The ideal outcome would be that people's tinnitus gets quieter. So that — just to be clear, this is not intended as sound therapy aiming to promote coping and habituation, this is aiming to suppress the loudness of tinnitus. I think if it has any effect there, then that's great and, you know, that really gives us something to run with. It may it may be that it doesn't. I've got three different slight variations on the theme to test, so there's always a chance that at least one of them does, but I really don't want to promise too much and risk creating false hopes because, as I say, there have been a lot of sound therapies tried. This is just one more to test, but, you know, if it works, the idea is to make this widely available. So, either once this is up and running — I don't want anyone to be too bothered about whether they get into initial studies or not — because if it works, there's going to be more, it's going to be widely available. No one's going to miss the boat as such.

### 1:04:46 The subtyping of tinnitus

**Hazel:** Okay, good to know. Where do you stand on the issue of subtyping? In recent years more and more researchers have started saying that if and when we find a cure it will actually be different cures for different patient groups because tinnitus is such a heterogeneous condition and you can't compare one type of tinnitus with the other. Would you agree with that?

**Will:** Yeah, this is a long-standing, raging debate. There is clearly at a minimum heterogeneity, so tinnitus does vary to some extent in its cause and certainly in the perceptual features and characteristics. So, does that mean that there's just a smooth spectrum across all these different factors? There's one condition that can just occupy different points or are there distinct subtypes that are just fundamentally different through all their mechanisms? I couldn't tell you anything authoritative on the subject. My feeling is that I'm quite content with heterogeneity rather than subtypes, unless compelling evidence comes along that there really are distinct subtypes that are just fundamentally separable throughout all levels of

the pathway. I can believe a sort of single middle common pathway that something perhaps again to the model I put forward in 2016 that is common to all tinnitus and then when you move a bit upstream from there in the causes, different balances of causes, different combinations, and then again, moving downstream, slightly different characteristics and reactions. I suppose whether you need different treatments for different ones without a case, it depends on are you intervening with that core bit of the mechanism that's common to all, or are you intervening with something a bit farther out that is just addressing one of many potential causes.

**Hazel:** Right. Something more peripheral perhaps, like a somatic tinnitus where you can resolve it by correcting a jaw issue or something.

**Will:** Yeah, I think that would be a very good example, which might not work on someone when there isn't any somatic influence there. So, I think that's a very open question — whether we need one or many treatments. It really depends on what those treatments are going to be and yes, subtyping versus heterogeneity, watch this space, really. It's a very difficult thing to prove because actually most studies will only show sort of group level differences and it can become quite artificial how you put your groups together, so it's a tricky thing to deal with.

**Hazel:** Yeah, I haven't heard one sort of authoritative concept of what the subtype categories then should be.

**Will:** No, no, and every time I'm at any venue where this is being discussed I sort of stick my head above the parapet and go well I'm not persuaded that subtypes exist; I'd like to see some evidence, and I have yet for this to be met with anyone claiming that there is solid evidence, so I think we just don't know. I'm just sharing a personal viewpoint. The thing I do occasionally take a bit of issue with is the argument that the treatments are there already and the reason they're not working is because of subtypes — that actually if we just matched our existing treatments correctly to the right people, then everyone or lots of people could be cured. A response I give to that is: show me the one person you cured and then we'll deal with why we're not curing everybody.

## 1:08:16 Difference between acute and chronic tinnitus

**Hazel:** That's a good one. Yeah, because those cases are few and far between and we see it on the **Tinnitus Talk** forum. Obviously, I don't have hard statistics but, I feel like we would see a lot more people there saying, "Okay, my tinnitus completely went away after trying this or that," and it just doesn't happen that often. Maybe a last question in terms of cures and treatments: would you view acute tinnitus and chronic tinnitus as two separate conditions that would require different treatments, and do you believe it should be possible theoretically to treat or cure tinnitus regardless of how long someone has had it?

**Will:** I see them as the same condition, but there may be some differences in the acute and chronic states. The reason I see them as the same condition is there's quite compelling evidence now that by the time tinnitus has been there for four weeks, unfortunately unless there's a reversible cause of hearing loss that happened at the onset like loud noise exposure

or an ear infection, you've only got about a 10% chance of it disappearing by 6 months and if it's there by 6 months, it's likely to continue long-term. Which is not to say anyone newly developing tinnitus to be put off. Obviously, there are naturally huge improvements for most people in awareness and suffering and distress of the impact of tinnitus. But I'm seeing them as the same condition.

Now, I do think that it's probable that there's a shift in terms of — probably what I'd call precipitating mechanisms that actually cause the tinnitus to occur to begin with. These are things that impact on sensory precision getting over that threshold, and then maybe perpetuating mechanisms that are to do with learning the tinnitus prediction and pattern over time. I think it might be hard to draw an absolute hard distinction. What you probably got is more of one of the beginning and more of the other later on, and then there is evidence showing that there are probably some brain network changes that continue to happen even after years with tinnitus. How critical they are to maintaining it, I don't know. It's hard to say.

I think everyone's working towards trying to come up with eventually ways of getting rid of tinnitus regardless of its stage, and I don't see anything that should make it fundamentally impossible to get rid of. That said, I think it's highly likely that if there are things that help suppress tinnitus, they'd be more effective in the early stages. It would be a bit weird if it wasn't. Certainly, if you look at the pain literature, there's overwhelming evidence for the benefits of painkillers in neuropathic pain agents for acute pain; for chronic pain the evidence is really not so compelling. They're still used, but actually I've got a number of colleagues in neurology who spend a lot of time just trying to get people off long-term side-effect-laden painkillers for ongoing pain that isn't responding to them, and when they managed it, the person is no worse with their pain but they're better with all the other side effects. So, I think it's a bit of both. I think if any of our existing drugs do work on tinnitus, they're probably more likely to be effective earlier on, but then I've also said at the same time I don't think any of the existing drugs we have a going to be that the ultimate tinnitus cure, which we're still working towards.

## 1:11:45 Research collaboration

**Hazel:** So Will, I'm mindful of having already taken quite a bit of your time on a Sunday morning. Maybe we can wrap up the discussion by talking a little bit still about collaboration within the research field with patients and funding issues and such. How do you see your work in relation to the overall tinnitus research community? Do you think there's enough collaboration there? Are there more synergies that could be leveraged?

**Will:** Yeah, I mean there's great things like the TRI, **Tinnitus Research Initiative**, you know, really established structures to get that box of research together with collaborations, common methods, and there's always more that can be done, but I think that's being really, really positive things person put in place to facilitate this. I speak with other people centers across the tinnitus field to share ideas, share methods and things, so I think it's all there. I think — I don't think there's much of people being too cagey with their ideas and methods and not sharing them so as to hold things back particularly. I mean I can see that if people are sort of in the middle of a clinical trial or something, they'll keep their cards close to the chest,

and just, well, that's running and that. More collaboration's always better. We don't so much need it to be able to run big studies because actually because tinnitus is common — there are so many people with it — is not like some of these rare medical conditions where you need huge international trials just to get sufficient numbers. And actually, people with tinnitus — it's quite inspiring how enthusiastic they are about taking part taking part in research, you know, everyone I've met seems to be with tinnitus really.

I think collaboration and talking, sharing, all of these things is all very important. Will it ultimately be what gives us the breakthroughs? Who knows? I think there's got to be enough collaborative thoughts or the people will sort of end up on the same page about things and not come into conflict too much and there has to be enough independent thought so people don't get sucked into the trap of accepting things as definitely true that aren't actually true or, you know, just following accepted wisdom too much. I probably collaborate less than I should and work a bit too independently. Whether that's a good or a bad thing or which side of the optimum I'm on, I'm not sure, but I probably tend to try to accept nothing is given and pursue my own ideas.

**Hazel:** Let's talk about us about collaboration with patients or people who have tinnitus. So, you actually came to us a few months ago seeking input from the **Tinnitus Talk community** for your new research idea. Why was that important to you?

**Will:** I think it's always important because as researchers, we can have an idea about what we think is important, but actually, at the end of the day, we are fueled by public money, donated money, the generosity of time and efforts of everybody who chooses to volunteer in research and for the benefit of people living with a particular condition. And I think a big part of it was wanting to check that actually people living with tinnitus thought that this was a worthwhile thing to be doing, was a worthwhile approach to take. I was aware that in my mind to really understand the bits I'm interested in of tinnitus, I think will make the difference, one needs to take a step back into basic science to an extent because there's parts or just normal functioning that are not sufficiently understood as well as a little bit of side step, as I was saying, into related conditions. So again, part of it is sort of checking that people wouldn't feel still think this is worthwhile, wouldn't feel short-changed at the widening the focus there.

And then there's more technical pragmatic matters about what it's like to be involved in the research, the methodologies, the methodologies used — actually just understanding the rationale for it, you know, it's not all about just the distant delivering of a cure, but the knowledge gained and what we can be reporting back to people that “hey, we're not there yet but we found this or we found that.” So, yeah, I think it was a number of approaches and then I, in fact, these people who think a lot about tinnitus and care a lot about tinnitus and I think it's important to value everybody's thoughts because everybody can have good ideas, and it's often only when you present things in a more open forum, you start opening yourself to just other ideas and things you wouldn't have considered otherwise.

**Hazel:** Yeah, we did a poll a year or so ago, which a few hundred people answered, asking them which stage of the research would you most like to see more patient involvement — you know so there's the initial, the research ideas, or the research agenda, then there's research design, then the clinical trials, then data analysis and communication of outcomes,

etc., so you've got the whole – all the phase of the research there; and overwhelmingly people wanted to be involved earlier on so actually at the very conception of new research ideas, and I thought that was a really interesting and telling outcome, and I think therefore all the more we appreciated you coming to us with a new idea and asking for input because what we see all too often is that patients do get involved or consulted but at a time/moment when basically the whole plan is already set in stone and there's not really any room for further influence there. That's what happens when we get invited to research consortiums like TIN-ACT and ESIT. Not that we don't value being a part of that — there is definitely a value in that — but we didn't get to influence the research agendas there, so that's, I think, we'd like to see more of that, so I think you are setting a good trend, hopefully, in that regard.

**Will:** Good. Hopefully, yeah. I think that's how it should be. There's much more room to influence things if you're involved earlier.

**Hazel:** Is there anything else that we as a patient community could do to influence the research agenda?

**Will:** I think it's really difficult. I think the biggest two things are: joining the campaign for increased funding and dedicated funding for research or clinical care for tinnitus, which is going on, and the other side to things is the harder one, which is getting more people interested in it, which is a sort of public awareness, you know, gradually fueling an increased public awareness of the existence of tinnitus, the impact, and the huge challenge in tackling it.

**Hazel:** Yeah. Yeah, it's definitely a challenge. We'll keep pushing, for sure, for that funding and increased awareness and attention. Will, I want to thank you so much for this very insightful discussion. Again, sacrificing half of your free Sunday, thank you so much.

**Will:** That's quite all right. My pleasure. My pleasure. It's Monday, by the way.

**Hazel:** Oh, it's Monday, yeah! You know what? I said Sunday before, didn't I? Yeah, so I took the day off from my day job, so in my mind it's Sunday because I don't have to work — yeah, and you have a regular day off, I think, for your family on Monday, correct?

**Will:** More or less, yeah. It's usually full of things that have to be done.

**Hazel:** Work anyway. Yeah. Exactly. All right, well then thanks for nevertheless for sacrificing your time.

**Will:** My absolute pleasure. Thanks for having me and thanks for a very enjoyable discussion.