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S2: Larry Roberts, PhD
S3: Dean Flyger, AuD

S1 00:00 Welcome to Conversations in Tinnitus a podcast of the American Tinnitus Association. The American Tinnitus Association is a non-profit organization dedicated to research, advocacy, education, and support for people who live with tinnitus. Conversations in Tinnitus podcasts are an extension of ATA's magazine, *Tinnitus Today*, the only publication dedicated to educating the public and practitioners about ongoing research, treatments, and management of the condition. [music]

S1 00:49 Welcome to another episode of *Conversations in Tinnitus*. I'm John Coverstone, along with my colleague and cohort, Dean Flyger. And joining us in this episode is Dr. Larry Roberts who is an emeritus professor at McMaster University in Hamilton, Ontario, and in his lab, studying neuroplasticity in tinnitus for many years now. And let me start just by asking you, Dr. Roberts, what is it that you're working on right now? Because seems like you're always involved in some of the cutting-edge research in the area of tinnitus.

S2 01:27 Well, thanks, John. It's a pleasure to be on the podcast. I hope it's useful for your listeners. Right now we're working on the problem of the role of hidden hearing loss in tinnitus and hyperacusis and also developing tools that we can use to detect hidden hearing loss. And the reason for focusing on hidden hearing loss is two-fold. While about 90% of people with tinnitus have hearing loss detected by the clinical audiogram, the standard test for hearing function, about 10% don't, and we want to understand this 10%. I think it's quite important. And another reason for looking into hidden hearing loss is that we really will not understand tinnitus until we know what causes it, and all the evidence is pointing to hearing loss. New cases of tinnitus, that is, tinnitus that occur in people who are in their 20s and 30s, and a surprising number of cases even in teens, have very normal clinical audiograms. So understanding the role of hidden hearing loss, hearing loss that's hidden from the audiogram, is really important for understanding what causes tinnitus.

S3 02:44 Interesting. So to ask a general question, are you going down the road of it being somewhat of a auditory neuropathy problem, something

that's a little bit higher up in the auditory system, or is it something that you may suspect is cochlear in nature?

S2 03:05 I think tinnitus is different from auditory neuropathy. However, both of those conditions involve changes in the brain. And in the case of tinnitus, those changes in the brain occur when the brain loses some of its input from the ear. So it's cochlear pathology, in my view, and the evidence for this is pretty strong that it's cochlear pathology that sets tinnitus in motion. But the tinnitus sound itself is actually generated, not by persisting irritative activity in auditory nerve fibers. It's rather generated by changes in the brain that take place when the brain loses its input from the ear. One thing I should add to that statement is that the input from the ear that matters for tinnitus is input that comes from the part of the ear that responds to very high-frequency sounds. So you can have reduced input over the auditory pathway that affects sounds that are high in pitch, and your speech perception or processing would be completely normal. So the hearing loss that's important for tinnitus is high-frequency hearing loss that doesn't affect speech that much. It does affect it a little bit. If you have trouble hearing speech in noisy environments, for example, it may be that you have some hearing loss in this high-frequency range. Because we need those high frequencies for really good processing in noise. But for ordinary conversations, like the ones we're having right now, we don't really need that high-frequency input. So to summarize the point I'm trying to make here, yes, tinnitus is caused by the changes that take place in the brain when the brain loses some of its input from the ear. And the specific input that's reduced or lost is high-frequency input, input generated by high-frequency sounds.

S1 05:17 So Dean and I recently were talking about some of the research that's emerging in hidden hearing loss, since you brought that up. In fact, I wrote a couple articles on this for *Tinnitus Today* as well, recently. And one of the lines of research which has emerged in recent years is synaptopathy, which is looking at the synapse of the cochlea and the auditory nerve and a breakdown at that point. Another one that came out real recently is demyelination, where a portion of the auditory nerve loses that myelin coating that helps it function well, function normally. Do we know the mechanisms yet of how things such as this are leading to tinnitus? Are we that far along?

S2 06:07 I think we're at the point where we can say that synaptopathy is a cause of tinnitus. And we know that these synapses that you mentioned, they're the connections between the auditory nerve fibers and the auditory fibers in the ear. Those synapses are vulnerable to damage by loud environmental sounds. But the synapses that are vulnerable are those, again, that convey high-frequency information in auditory pathways. It's the synapses that convey this kind of information from the ear to the brain that are most vulnerable to damage by environmental sound. And they also are affected most by

aging. So these observations all fit together and point to this form of synaptopathy as being very important in tinnitus. Myelination could be a factor. We're not able to discriminate between these two things in our laboratory, but we do have techniques that can allow us to infer the pattern of auditory nerve fiber damage that leads to tinnitus. And our tools, again, point to damage to these synapses that convey high-frequency prevention. So synaptopathy, a very important part of the picture.

S3 07:31 So clinically, speaking as an audiologist who sees patients, evaluates patients, what are some of the tests that we can use now to start to identify hidden hearing loss? Do we need to do high-frequency audiometry? Do we need to be more diligent with speech and noise testing and gap detection testing? Do you feel like there are any tests that can be helpful to us now to start solving that problem from the clinical level?

S2 08:08 The edge of the field right now is working on tools for the clinic that will address the problem you raise. Given what we have right now, I think you've mentioned two procedures that can be useful. One of which is-- for tinnitus, I think it's important to measure the extended audiogram up to 16 kilohertz in the clinic. Usually, we stop at 8 kilohertz. But there are a lot of people who have very healthy audiograms up to 8 kilohertz and they still have tinnitus. If you look at the high-frequency audiogram, you will see some high-frequency loss there more so in people who have tinnitus, than in people who don't. So yes, I think the extended audiogram is one tool that should be used in the clinic. And the other is speech in noise. I think that's an important tool. And the reason for it is that people who have tinnitus also have problems processing speech in noisy environments. They have some temporal processing deficits. And those temporal processing deficits, as well as the tinnitus, probably rely on the same auditory pathways. Again, we're looking at the auditory pathways that transduce high-frequency sounds and the synapses that are important in those pathways that connect the auditory receptors to the brain. Well, those are the two methods in the clinic right now that are useful, but there are others that are under development. There are other techniques for measuring the health of the auditory nerve that are a little bit more invasive [laughter]. They involve putting an electrode on the eardrum . But there's some pretty good evidence that people who have tinnitus will show some abnormalities in the auditory nerve, but with this technique.

S2 10:08 Another technique uses EEG activity, electroencephalography. This is what we do in our lab. Actually, we do both of these in our lab, but we've done more electroencephalography. Let me just call it EEG, recording brain waves from sensors on the scalp. We've done this quite a bit in the laboratory. And you can use stimulus procedures and signal processing methods that will allow you to look at activity in very early

auditory pathways. And these EEG signals are also abnormal in tinnitus. So that's another technique coming down the pipeline. So there are two methods. [inaudible] auditory nerve activity from sensors placed right on the ear drum and then measuring activity in early auditory pathways using EEG. And then, of course, there's speech and noise as you just mentioned and the high-frequency extended audiogram. The problem with these methods, though-- well, in the first place, the EEG and cochlear measures haven't been developed enough yet to be useful in the clinic. But for any method to be useful in the clinic, we need norms. We need to know how discriminating the measurements are, and that requires large database. And we're some way away from having norms that will allow you, with great reliability, to distinguish between people who have tinnitus and people who haven't. I don't want to ramble on here too much, but I think another measure that's useful in the clinic is to measure loudness discomfort level, and I can tell you why I think that's important. I don't want to end up giving a lecture here [laughter] [crosstalk].

S1 12:12 No, no you're fine. Go ahead.

S3 12:14 You have a captive audience [laughter].

S2 12:17 Well, let me mention the study that we've done in Sao Paulo, Brazil. And I say we-- it's not actually my lab. It's the laboratory of Tanit Sanchez. Dr. Sanchez directs a tinnitus clinic in Sao Paulo as part of the University of Sao Paulo. And she and her team carried out a remarkable study of the problems of tinnitus in teenagers enrolled in a private school in Sao Paulo. And she studied a lot of teenagers, 170 teens. And 28% of these teenagers experience a persisting tinnitus that could be psychoacoustically measured in a sound booth. And the Sanchez group measured their audiograms up to 16 kilohertz. They were completely normal. That is, the teens who had tinnitus had audiograms that were indistinguishable from the teens that did not have tinnitus. Well, that won't surprise audiologists because teens have really healthy audiograms. They also measured something called otoacoustic emissions, which, of course, you know about, although perhaps our listeners don't. The ear actually emits sounds. The sounds that the ear emits are very low level so we can't hear them, but they can be detected by putting a microphone in the ear. And these sounds called otoacoustic emissions tell us about the health of the auditory receptors.

S2 13:50 The teens with the tinnitus had auditory receptors, otoacoustic emissions, that were completely healthy. Again, you could not tell the difference between teens with tinnitus and teens without on the basis of either of these measures, the audiogram or otoacoustic emissions. Their ears looked healthy, but the one measure that did discriminate between the teens with tinnitus and the teens without was loudness discomfort level. And to measure this, the audiologist turns up the loudness of the sound until the point where the teen says, "That's an

uncomfortable loudness." The teens with tinnitus had loudness discomfort levels that were 12 dB lower than the teens without tinnitus. That's a lot. That means that a sound that an ordinary teen would find fine, would have to be decreased by 12 dB before the teen with tinnitus would say it was fine. They had reduced sound level tolerance. That's what discriminated the teens with tinnitus from those that didn't.

S2 14:59 And the reason I think that's important for the clinic is that when neurons and auditory pathways lose their input from the ear, they compensate for that by increasing their gain. And that increased gain probably is the reason why many people, and I think, actually, almost all people who have tinnitus have some hyperacusis. So these teens were giving us some evidence of hyperacusis, and that to me was an indication of the possibility of the synaptic damage in their auditory pathways. So there may be some hidden hearing loss in these teens, and the measure that seemed to pick it up was loudness discomfort level. I need to say something else at this point, too, because I know there are going to be listeners here. 28% of these teens did have tinnitus, but the Sanchez group followed them up for a year later and about half of these cases of tinnitus resolved. The tinnitus was gone. The other half, the tinnitus was still there, very low level. It didn't bother the teens too much. They said it would bother their concentration and their sleep a little. But the important message there is that new cases of tinnitus, especially in young people, over time can resolve and frequently do. Although, later in life, they may be at greater risk for the tinnitus returning.

S3 16:35 That's actually one of the very few bright spots we've reported with all of these interviews and conversations about tinnitus. If you're young enough, it can get better [laughter].

S1 16:47 Oh, I believe that--

S2 16:47 [crosstalk] tinnitus--

S1 16:46 --the cohort that you used for that study were at-risk teens, weren't they?

S2 16:56 Their risky listening habits were universal.

S1 16:58 Oh, okay.

S2 16:59 Everybody went to rock concerts. Everybody wore earbuds. And what was interesting about the teens who had tinnitus is that their questionnaire data indicated that they tended to be somewhat more protective of their hearing than the teens who didn't have tinnitus. So, yes they went to lots of concerts. Everybody used earbuds. But when they went to concerts, they didn't stay quite as long, and when they listened to music through their earbuds, they tended to choose volume levels that were a little lower. They seemed to have some awareness of

their increased sound level tolerance. When I say awareness, I'm not saying that they were actually conscious of it, but they were sufficiently aware of it to at least report it in a questionnaire. They didn't say, "Oh, I know that my sound level tolerance is reduced." They would never say it, that's a technical term. But they might say, "Well, when I go to a party, I usually stay there about an hour." Whereas the other teens would say, "Well, I usually stay there over three hours." So when I say they had an awareness, it affected their reporting behavior. It didn't necessarily mean they were consciously aware--

S1 18:19 So--

S2 18:21 --that tolerance was reduced.

S1 18:23 So that brings to mind chicken and egg, cause and effect. Did you get the impression that that group of teens with tinnitus who were, shall we say, subconsciously aware of this decreased sound tolerance, do you think it was because of the behavior that had led to this condition, and they were aware of it at that point? Or did you get the impression that maybe they were already someone who had some-- I don't know. I guess I'm thinking of maybe a predisposition or had some makeup that might have led them to more easily get tinnitus, and somehow that influenced their behavior. Was this a result of all the noise? Or was this maybe something that they came in with?

S2 19:13 That's a really good question. And the take that we advanced in the article - and one can only make an educated guess about this - is that the teens who had tinnitus may have had tinnitus and reduced sound level tolerance because they were more vulnerable to the sounds that they heard. All these teens heard a lot of sounds, and the teens with tinnitus seem to hear, maybe, some of these sounds at a somewhat lower level, or maybe somewhat less often. So it didn't seem to be excessive sound exposure that caused their tinnitus and their reduced sound level tolerance or hyperacusis. Rather, it's seemed to me that they were more vulnerable to the sounds that they heard. And what is the nature of that vulnerability? We do not know.

S1 20:06 Right. Yeah, I don't think we're anywhere near describing that, but I've certainly seen that in my clinic. I see a lot of US veterans, and you can sometimes have someone, say maybe an older veteran, they worked in artillery when they were in the army, and they have no tinnitus. And then you could have someone who was carrying the mail and was just occasionally exposed, but they went through basic training maybe even, and just on the firing range and the exercises they did during basic training, that brought on tinnitus. So it would be nice if there were a test we could give people to determine what their susceptibility was, but that's one area of research I don't think we've even considered tapping yet because we just aren't there.

S2 20:58 Well, when I say the nature of this vulnerability is a mystery, I should

say I don't know what the nature of this vulnerability are. But there are other scientists who study this area, and there are genetic factors that affect hearing. Quite a few genes are involved. I'm just not expert enough to go into that area. So I think something is known about this vulnerability but really not very much. What's interesting in your comment, John, is you've had people who've been exposed to explosive noises, and some get tinnitus and some don't. And what's the difference between them? That's a really good question. But it's also quite possible that exposure to these explosive sounds does induce some synaptic damage in auditory nerve fibers, but not enough to actually generate tinnitus. It may increase the risk that tinnitus will occur later on. There's a lot of audiological evidence that noisy exposure increases or accelerates the rate of aging in our ears. So the person who's had those explosive exposures may still have some increased risk, but it may take some time before it materializes.

S1 22:22 Well, and we've talked quite a bit with Jinsheng Zhang last episode about some of the mechanisms. We were talking specifically about neuromodulation. But that, of course, brings up a lot of neurophysiology, how the brain works when we have tinnitus, how it's responding or how potentially things are going wrong, so to speak, to cause tinnitus. Do we have any evidence that you've seen that maybe people's brains are responding differently to this trauma? For instance, some recent research I read, and somebody was looking at stimulating the dorsolateral cochlear nucleus because we have some evidence that that gating system, which may normally inhibit certain sounds coming into the auditory cortex, possibly isn't working correctly. That's one theory. And then maybe now it's allowing sounds in that it otherwise wouldn't if it was working correctly. And that's tinnitus, perhaps. Maybe you can correct me or expand even more on that. But is it possible, do you think, that just these noise exposures, this acoustic trauma, is affecting different people in different ways, and so it leads to different effects?

S2 23:36 I think neuromodulation is likely to be part of the picture. But you also mentioned the dorsal cochlear nucleus. Let me just refer to it as the DCN. It's a lot easier to say that. This is the first--

S1 23:50 Yes, it is.

S2 23:51 --nucleus in the auditory pathway. This is the part of the brain stem that first receives input from the ear by auditory nerve fibers. And tinnitus-related neural activity is first generated in this structure. And several groups have worked on this problem. The most prominent ones are James Kaltenbach, who is actually Jinsheng Zhang's PhD supervisor, and also Susan Shore. And Dr. Kaltenbach was at Wayne State University in Detroit. Dr. Shore is at the Kresge Hearing Institute in, I think, University of Michigan in Ann Arbor. They led the way on studying the role of the DCN in tinnitus. And there are two neural signatures that appear in the DCN in animals who show behavioral

evidence of tinnitus. One is an increase in spontaneous activity in neurons in the DCN, but the other is an increase in their synchronous activity in the DCN. This is correlated activity amongst the neurons. And these are widely regarded as two neural signatures of tinnitus, increased spontaneous activity in the DCN and increased synchrony in the DCN. And I think it's the synchrony that's especially important for the perception of tinnitus. These two changes tend to go together, but we perceive sounds when auditory nerve fibers fire-- or when auditory neurons fire together, when they fire synchronously. So this is one good reason to think that synchronous activity in the DCN is really the first step toward the perception of tinnitus.

S2 25:39

Now these two changes taking place in the DCN, the increased spontaneous activity and the increased synchronous activity, are the result of neuroplasticity mechanisms that are working in the DCN. One form is called homeostatic plasticity. And that form of plasticity makes neurons that have lost their input from the ear more sensitive to the inputs that they receive, and the other is something called spike-timing-dependent plasticity. That's a real mouthful [laughter]. This form of plasticity governs how neurons communicate with each other. And basically, this form of plasticity, spike-timing-dependent plasticity, can be summarized by a simple rule that neurons that fire together, wire together, and those that are out of sync lose their link. So this form of plasticity governs the synchronous activity in the DCN. Now both of these forms of plasticity, but especially this spike-timing form, are sensitive to neural modulation. And neural modulators are expressed in the DCN as well as right up the auditory pathway into the auditory cortex. So it's just a hypothesis - but it's a reasonable one - that maybe one of the differences between someone who gets tinnitus after a noise exposure and someone who doesn't may be that their neural modulatory systems are just more easily activated and driven. It's a total guess, but it is possible to tie neural modulation, and neural plasticity, and tinnitus together. And there's a large literature on plasticity in the brain and the role of neuromodulation in that plasticity, and it's quite important. So, yes, this is the reason for thinking that neuromodulators may be part of the reason why some people get tinnitus right away and others don't and maybe never do.

S1 27:46

Well, and then you also just mentioned an increased sensitivity of auditory nerve fibers or nerve bundles in that area. Does that tie in with what we were talking about earlier in the teen study?

S2 28:01

I think so. I think that increased sensitivity produced by homeostatic plasticity underlies our perception of loudness. So the increased sensitivity of the auditory pathway may underlie hyperacusis, whereas the increased neurosynchrony is responsible for the tinnitus perception, the tinnitus [inaudible]. But those two changes tend to go together because both take place when neurons in the DCN lose their input from the ear. Technically speaking, when they're deafferented.

S1 28:40 Well, and I just realized I may have mixed up a couple of studies. And this is because we're stretching the limits of my background in neuroscience [laughter]. But I think one of the studies I was thinking of and mixing up, perhaps, with what we had talked about last time with Doctor Zhang, was another one that was looking at the prefrontal cortex. And that's where I was thinking of the gating mechanisms that happen for sensory input. And so it's a whole ‘nother theory about the mechanisms that may be underlying these phenomenon in tinnitus in particular.

S2 29:16 Well, there is a theory that, yes, there are mechanisms in the brain. And frontal cortex and something called the subcallosal region are often implicated in this theory. They're the structures that are thought to be involved in gating. And there may well be individual differences in the extent to which we can suppress our awareness of unwanted sounds. That might be one reason why some people are more disturbed by their tinnitus percept than others. Maybe these frontal striatal gating mechanisms aren't as robust for those people who are more disturbed by their tinnitus and find it more disruptive of their attention. So that's a possibility. One thing we know about those mechanisms is that, generally speaking, there are three networks in the brain that are active in tinnitus. There's the tinnitus network, which is in the auditory pathway starting in the DCN, going right up to the auditory cortex. Of course, those networks speak to other networks in the brain, too, particularly involving memory and attention. So all of those systems are involved in tinnitus. And when you do brain imaging, comparing people with tinnitus to those without, you do find changes in the auditory pathways, but you also find changes in these attention systems and these memory systems.

S1 30:52 Yeah. Absolutely.

S2 30:52 And I think that's because when we process sound, we activate memory systems and attention systems as a part of normal information processing. So the fact that these other systems are active in tinnitus is not pathological. It's part of normal auditory processing. It's just that in tinnitus this processing is driven at low level, kind of continuously, by the persisting tinnitus neural activity in auditory pathways. So, yes, these other brain systems are involved, and attention systems are certainly part of the picture.

S3 31:33 So just a simple question and kind of circling all the way back to the front. So assuming that we can better identify hidden hearing loss that can be a main contributor to this cascading effect, which turns into tinnitus that is affecting this patient, has anybody started to give any thought about any kind of treatment?

S2 32:07 Yes. Two would come to mind in particular. I'll mention three. John mentioned transcranial magnetic stimulation. This is a technique that is used that injects magnetic pulses into the brain. It's painless. This is not

an immersive procedure [laughter].

S3 32:32 That's good.

S2 32:33 Yeah. Those magnetic pulses will disrupt tinnitus-related activity in places like the frontal cortex and secondary auditory regions. But the relief is not very long. It's maybe on the order of a minute or so. So it's not a curative treatment. But that is one treatment that a lot of people are exploring. A second category of treatment are procedures that are designed to harness neural plasticity, and Dr. Shore's lab at the University of Michigan has worked on this topic. The DCN also receives input not just from auditory pathways but also from somatosensory pathways arising from the region of the face, the thorax. Those somatosensory inputs feed into the DCN, and the auditory inputs feed into the DCN as well. And if you pair somatosensory and auditory stimulation at a very close timing interval and in appropriate order, you can actually suppress spontaneous and synchronous activity in the DCN. So this is a potential treatment for humans, and there has been some work done on this, and it's looking positive.But again, you're using neuroplasticity mechanisms to suppress the tinnitus.
The deafferentation is still there. So the plasticity will suppress the tinnitus for as long as it lasts, but eventually, the tinnitus will come back. So they might need some refresher procedures to suppress their tinnitus. But this could be a clinically beneficial tool. It's not in the clinic yet, but it's something on horizon.

S2 34:30 And the third thing I'll mention, which I think is most important, but about which we know the least at the moment, are procedures that will rescue damaged synapses on auditory nerve fibers. Some species will show spontaneous recovery of damaged synapses but not full recovery, but some of them will recover. Other species, this doesn't happen. We don't know where humans are on this dimension. But it has been shown that if you put neurotrophins right on the eardrum, that can promote the recovery of damaged synapses. But these applications are a long way removed from the clinic. And given that hearing loss is the trigger for tinnitus, the really important avenue of intervention here is to prevent hearing loss. And for this, we need to talk to teenagers and parents. But I think this is one reason why the work that's been done in Sao Paulo is so important.

S1 35:40 We have been talking with Dr. Larry Roberts who is an emeritus professor at McMaster University in Hamilton, Ontario. And we welcome the wealth of knowledge and experience that you bring us from your research in the areas of neuroplasticity and tinnitus and thank you for joining us here on Conversations in Tinnitus.

S3 35:59 Excellent summary. [music]

S1 36:17 The American Tinnitus Association is a nonprofit organization dedicated to research, advocacy, education, and support for people who live with

tinnitus. Gifts and donations to ATA are used to support research for a cure and other critical missions described on our website at www.ata.org