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Conversations in Tinnitus with John Coverstone, AuD, and Dean Flyger

Featured Guest: Phillip Gander, assistant research scientist, Department of Neurosurgery, Univ. of Iowa

- S1 00:00 Welcome to *Conversations in Tinnitus*, a podcast of the American Tinnitus Association. The American Tinnitus Association is a nonprofit 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 back to *Conversations in Tinnitus*. I am John Coverstone, as always, and across from me here is Dr. Dean Flyger. And joining us for this episode is someone, believe it or not, you've heard about before in one of our podcasts last year. And so now we're actually talking to the person himself doing the research. And this is Dr. Phillip Gander, who is an assistant research scientist at the University of Iowa. And the study that I just mentioned was one where we talked to your PhD advisor last year, Larry Roberts, and he referenced some of the work that you've been doing with epilepsy patients who have a craniotomy and will allow people to go in and do direct brain measurement in multiple areas; but, you've done some in tinnitus, and so that's why we talked about that. And you were just telling me, as we were preparing to record here, that you have some updates on that and that you're continuing to do that research. So why don't you go ahead and give us the updates and tell us what you're doing.
- S2 01:51 All right. Well, thank you very much for inviting me. Yeah, the work that I do here at the University of Iowa is pretty exciting. It's a relatively unique opportunity to work with these epilepsy patients. And my experience is that the people of the American Midwest are incredibly gracious and willing to help out with research. So, because of that, I've had the opportunity to work with a couple of people who've happened to have tinnitus in addition to also being present here, being investigated for epilepsy. So, what I did in a previous report – or for the previous experiments – with a patient that was reported a couple years ago now, I was able to employ what's called a residual inhibition paradigm in which I played a white noise, sort of semi-masking sound so it covered up partially, or almost entirely, covered up the tinnitus while the sound was playing. And then what happens, after you turn off the sound, is that, in some cases, some people experience a slight reduction or an elimination of their tinnitus for a brief period of time. So, it's not really a useful treatment, of course, because you replace one sound with another sound. But as a neuroscientific tool, it's pretty useful because we're directly manipulating the tinnitus percept itself. So, then all we simply did was ask the question, "What are the correlates in the brain that we get when we change someone's perception?"
- S2 03:36 So due to complete serendipity, as often happens [laughter], I had this beautiful experiment all laid out beforehand. I saw the patient before he was implanted with the electrodes. I found sounds that made his tinnitus quieter, control sounds that did nothing, sounds that made it louder. And after he got implanted, a lot of that went out the window, which was rather frustrating. But we also played around with white

noise, which was not as effective in inducing residual inhibition or making his tinnitus quieter, but it did still do so. And the serendipity came in the fact that this exact same sound, half the time made his tinnitus quieter and half the time did nothing. So, it was its own perfect control. And so all we did then was look at his behavioral report when he said, "Yeah. My tinnitus got quieter," "No, it stayed the same," and we just correlated the changes in the brain when he said it got quieter as compared to when nothing happened. And what we found was a rather large distributed network of activity throughout the brain, at least in the electrode locations where we had brain sites implanted for investigation for the epileptic focus. And this included areas, not surprisingly, in auditory cortex but also in sort of higher level auditory association areas, in classically emotional areas for attention. Anyway, the point being that we didn't set out to try and replicate the studies that are done with noninvasive brain imaging, for example, with fMRI, but we pretty closely replicated those findings, which is a nice win for science. But as we were kind of talking about earlier, it might not be such a great win for patients and for ideas about treatment.

S2 05:57

So more recently, as is usually the case with scientists, they are very loathe to allow a publication on a single sick subject [laughter]. I hope someone who was a reviewer is listening to this podcast. We had no end of trouble with review. And in the end, the other reviewers and us sort of beat down one holdout reviewer, and it got published in the journal we ended up getting it published in. Of course, I think it was a good study. It was really well controlled, but it does hold the sort of fundamental scare for scientists with reporting results from a single person. And this person had sort of as generic tinnitus as you could possibly imagine. Maybe it was like a bilateral tonal tinnitus caused likely as a result of noise-induced hearing loss and was mildly bothersome, so pretty generic, and so we commented about that. But still we always want to try and replicate, and of course, we want to replicate our own science or other people have replicate our science. So, I've seen a number of scientists at meetings who said, "Hey, Phil, you got to redo those analyses. Find someone else." Of course, that's not that easy because 10, 15 percent of the adult population of the epilepsy patients might happen to have tinnitus, and so it's not that often that we actually get one of these people coming through the door.

S2 07:40

But I did actually happen to have that opportunity last year with a woman who happened to just be a really reasonable match in terms of age and type of tinnitus, again it was tonal, and it was-- she had sort of later onset in life. I don't think she had a clear onset cause picked out, and her hearing was actually a bit better. So more normal within the sort of typical audiometric range. But still she, of course, had some high-frequency hearing loss above eight kilohertz, especially. And so I basically just ran the same study. And played for her a white noise again. And looked at her behavior report. And again, this is not my choice. She, about half the time, said, "It made my tinnitus a bit quieter. And the other half the time, it didn't do much." I haven't yet analyzed the data to actually see if we found the same sort of patterns in the brain, of course. And that's the million-dollar question that the other scientists have. But one of the really exciting opportunities, that I guess Larry might have alluded to, that I was able to do with this patient and not with the previous patient is that we were able to directly stimulate at the electrodes in the brain. And so we do this in a sort of controlled way so that we obviously don't cause a seizure as a result of our electrical stimulation. But all I was doing – of course, we were recording from these electrodes at the same time, but I was also just interested in sort of her behavioral report as a result of having electrical stimulation at certain key sites in her brain. I guess I should back up for a second.

S2 09:43

These people typically have around 200 electrodes implanted. So, there's not enough time to sort of go through exhaustively and test every electrode as, of course, as the evil scientist in me would want to do. So, you have to [laughter] pick a few key targets. And the obvious key target here – because we, uniquely in the world, implant this electrode along the long axis of Heschl's gyrus, which means that we have a sampling of core or primary auditory cortex and then also the surrounding sort of non-core auditory cortical regions. And so there are obvious, many hypotheses or theories about tinnitus generation that involve auditory cortex; at some level, of course, it must. So, if we simply play around a little bit in auditory cortex or primary auditory cortex, what do we see? So, I was face-to-face with her. And in a relatively unblinded way, flipping the switch on the stimulator. And so I was directly stimulating her brain. And when this happened, at first, she had some strange perceptions, which we can often get because we have some idea about where our electrodes are, but we don't know exactly where they are. And exactly where they are really matters. And so you can get wildly different perceptions or no effect, depending on exactly where your electrode is.

S2 11:17

And so she had some sensation that kind of moved across her face and then shot down her chest, down her body. And so I didn't want that to happen again. So, I backed away from that electrode [laughter] immediately. And that was likely stimulation at a site closer to sort of a sensory integration region called the insula, which is sort of medial to a Heschl's gyrus and auditory cortex. So, it was in the region. It was just not exactly the right spot I wanted to target. So, I backed off just one electrodes – and these electrodes are spaced a few millimeters apart – and stimulated again, and immediately caused her tinnitus to decrease. And this was really interesting. And so she reported that her tinnitus got quieter. It did not go away entirely, but it got quieter in the same way that I made her tinnitus quieter with these residual inhibition-inducing sounds. So that was really interesting. And she did feel it was qualitatively different. And I think that's not surprising because these were very different mechanisms in terms of disrupting or changing activity in auditory cortex. One of them, of course, is the naturalistic way of feeding sound from the ear up into auditory cortex. And the other way was directly causing electrical activity to group some large amount of neurons, likely very different than we would normally recruit with auditory stimulation. And so she reported longer lasting residual inhibition as well. So before, it was only seconds to 10 seconds. This was 30 seconds to then minutes. And then I was [crosstalk].

S1 13:08

With the electrical stimulation?

S2 13:10

With the electrical stimulation.

S1 13:11

Yeah. Versus [crosstalk].

S2 13:12

So, then I was starting to run into the trouble with time. Right? Because I wanted to have her tinnitus sort of recover to the normal perceptual level, and then stimulate again, either with different amplitude, or a different frequency, or a different site. So already now you're getting a sense for how there's not enough time to basically try and do everything I might want to try and do. But I sort of marched along the Heschl's gyrus electrode and continued to get throughout all of the sites that I stimulated, that definitely spanned from core auditory cortex to non-core auditory cortex, so spanned this boundary. I got very similar effects. So as a scientist, I might have maybe wanted more specific results, but still I'm going to take the ones I got, which were very exciting. And the other thing that immediately jumped into my head, of course, is that, "What is her regular auditory processing like at the same time that I'm

stimulating her brain?" And, so after a few trials, then I started talking to her while I had flipped on the stimulator. And basically just saying, "How's my voice? Do I sound the same?" And we carried on a small conversation while I was stimulating her brain. And there was no change. She reported no change in her actual regular auditory perception. But she was also experiencing this inhibition of her tinnitus.

- S2 14:42 And that result, for me, was very interesting. And for me, was kind of a final nail in a coffin for a sort of motivation. For some auditory scientists, like myself and Larry Roberts, maybe, when we started studying tinnitus was that another sort of attractive thing for an auditory scientist is that, if we can understand how maybe a phantom sound is generated in the brain, we can understand more about auditory perception just in general. And so fast-forward here 10, 15 years, and I'm flipping the stimulator. And then this person's having regular auditory perception, but a complete dissociation with respect to the sound of her tinnitus. For me, that was pretty conclusive that these things are not the same. And maybe that's not surprising. But I think I really want to get that result out there to the scientific community because I think there are many people – and there probably will still be people who argue with me – that might hold that there might be some still relation between regular auditory perception and the perception of tinnitus.
- S1 15:54 Are any of those electrodes measuring brain activity, or are they just there to stimulate?
- S2 16:00 No. So they are all – they can do both. But they're all implanted for purposes of measuring seizures – seizure activity, and seizure focus. And so I can, when I stimulate at the electrode, I can simultaneously record at the neighboring electrodes. But all of those neighboring electrodes – the immediately neighboring electrodes – are highly contaminated by stimulation.
- S1 16:25 By the stimulation. Yeah.
- S2 16:26 ...artifacts. The electrode artifacts generated by the stimulator kind of swamps out a lot of activity that you might be interested in recording. So, there again, that's like a sort of classic problem here. Of course, I want to be recording from exactly the location where I'm stimulating. But with the type of electrodes that we have implanted that's not possible.
- S1 16:49 Sure. Okay. Yeah, because I was kind of wondering if there was a way to compare directly on the site – at Heschl's gyrus – compare the auditory stimulus to the electrical stimulation and measure how different those were at that site with those different results that you got. But I can see how, yeah, that would be a difficult near-field measurement, at least, to make.
- S2 17:13 Yes. Yeah, yeah. But of course, we have other areas of auditory cortex that are implanted so that we typically have electrode grid arrays implanted over the sort of lateral convexity of the temporal cortex. So, all of the lateral superior temporal gyrus, all auditory cortex is covered, and so we would be able to record from there definitely. And those are definitely, again, brain locations that we have found that are involved in generating the tinnitus percept from our previous literature.
- S1 17:49 Right. Well, and as you said, they kind of have to be. If you're at the cortical level, if we perceive it, we have to have stimulation there [laughter]. That's kind of a basic tenet, I think, of tinnitus.
- S2 18:04 Actually, I'll propose something sort of interesting in that regard. So you may have heard about a lot of ... increasingly research seems to be finding what might be more

classically considered memory areas of the brain, including hippocampus and the parahippocampal gyrus, are seeming to pop up in some of these neuroimaging studies. And I'll admit my relative ignorance about the animal literature about how much they're finding there. But the idea here might be that – as we've proposed in our first epilepsy patient report – that the signal coming from these memory regions may, indeed, in fact, be some sort of perceptual memory for the tinnitus itself. So, I'm not necessarily proposing this, but you could imagine a crazy scenario in which you could be – well, we know this is the case, actually, anyway. You could be completely deaf and having no auditory stimulation or no regular auditory processing in your auditory cortex, yet you hear a tinnitus sound. We know that's the case, yeah.

- S1 19:13 Yeah. We know about that.
- S2 19:15 So where is that sound coming from? Right? Where is that being generated? Because it's not necessarily being generated in the auditory cortex, although it could be.
- S1 19:23 Maybe. Yeah. We don't know.
- S2 19:27 So, there may be something else there with respect to these larger brain networks that may, indeed, play a role in sort of the permanence of the tinnitus itself and its relative imperviousness to treatments that are sort of targeting, say, auditory cortex, specifically, to try and change the things that are going on.
- S1 19:53 Yeah. Well, and clinically we see patients, occasionally – we had this conversation with David Bagley. I don't actually remember which podcast it was on now, but ...
- S3 20:04 That would be the first one [laughter].
- S1 20:05 Well, if it was this one or another one.
- S3 20:06 That was the very first one.
- S1 20:08 But he made the comment that we occasionally will see patients, and they might tell you, "When I first get up in the morning, I don't hear my tinnitus. And then I kind of sit there, and I kind of think about it for a while, and then it comes back." And we're waiting for more studies to look at this kind of thing and look at auditory memory and the role that it might play. And this is actually a nice segue into the other thing that I wanted to talk to you about because we have seen some neuroimaging studies tell us that that area lights up in some people with tinnitus. So, we can't clinically make too big of a leap yet, but there does seem to be some anecdotal evidence that supports that theory that auditory memory may play a role in tinnitus for some people. And to make that segue then, something that I really wanted to talk to you about, as a neuroscientist who's done a lot with neural imaging. Dean and I have talked, almost ad nauseum over the years, about the vast array and how it seems like every three to six months there's a new study that comes out that finds tinnitus somewhere new in the brain. And in all these multiple sites of activity using fMRI or other measurements. And I know that you've done a lot of that, and you certainly follow that research closely. And I think that would be a really interesting conversation to have about these different sites of tinnitus, and what we're seeing in the literature, how viable some of that is, and what that means to us.
- S2 21:47 Right. So, I think for your audience, I think it's the thing that I've been trying to say publicly at various talks and presentations that I give is that we do need to be very wary with respect to the tinnitus literature in general and especially in regards to what you're saying. It seems that as many studies as there are, there are different findings with respect to where in the brain tinnitus might be generated. Although I guess, to be fair, there are some now consistent findings seeming to pop up by some

of my colleagues that use fMRI, resting state fMRI, to try and investigate tinnitus correlates. But the thing to keep in mind, I guess, for all of this sort of stuff is what is the tool? What is it measuring? And what are the sorts of conclusions you can make? And when I started studying tinnitus specifically, when I was working as a postdoc in Nottingham, England, sort of embarking on a study for fMRI for tinnitus recording – and this was starting in 2009 – I was looking at the literature and exactly as you just [inaudible] ... what are the sort of targets that we might want to look at? And everything in the auditory pathway at least was lighting up, so to speak, as a potential target.

S1 23:23

Yeah. And a few other things as well [laughter].

S2 23:26

Yeah. A few other things as well. Especially, since that time, the numbers of brain regions has just increased. It's not become more specific. And yeah, here, I'm reading a note that I have here, and I think this actually really speaks to this point. So, at the time, in around 2009, when I was doing a sort of literature search ... that half the number of all the articles with the keyword "tinnitus" that had been published in 2009 was added, again in so sort of in my time, what about eight years later. So, the research effort essentially doubled, and nothing new, really clear, has come out as a result of this rather large increase in sort of research activity. And that's a bit daunting. And the networks that are being proposed and different theories then come out by each researcher about different brain networks. And so as an audiologist or as a clinician, how do we go ahead and try and tease this apart? And one thing we need to be mindful of is what are we able to conclude, right? So, we want to try and be clear that are we able to dissociate the factors that are sort of causing the tinnitus as compared to those that occur as a result of the reaction to the tinnitus. For example, distress. So, if we were instead measuring phantom-limb pain, right, someone's distressed as a result of their pain, and they are going to have a, let's say, pain-network light up in their brain, does that mean that that's the tinnitus network? No. Did it happen in the tinnitus population compared to your control population that didn't have tinnitus? Yes. Yes, it did. So, does that mean it's tinnitus? Well, no, of course not. But I made this comment actually a couple of years ago at a conference. And one of my colleagues, who is a tinnitus fMRI researcher, said that I have to allow for the logical possibility though that the reverse is also true. Right? That the reaction to the tinnitus could also be a causal factor in the person's sort of sustained or chronic tinnitus, right. In the chronification of someone's tinnitus. That might still logically be the case. And I think that's true. So, we should be careful about that.

S2 26:24

But the other thing that we really want to be clear of, and it's just the case with all of science, but it's just particularly true of a lot of the tinnitus researchers, you have to be careful about what controls have been done for the study. And so we talked about, to be fair tinnitus researchers though, that there's been a moving target with respect to what all the measures might be that you want to include or control for. So key ones that have come up and sort of shot down some of previous publications include hearing loss and hyperacusis. So, these sort of comorbid factors really need to be accounted for in your control group. And so in the extreme then, a PhD student and I published some of my early investigations using resting-state fMRI with the general sort of attractive hypothesis that tinnitus is always going on. We are going to see some signature of that in the sort of ongoing activity of someone while they're at rest. And when we controlled for factors like hearing, and gender, and no one had hyperacusis, we did not find any group differences. So, our study stands among a few, not the majority of studies, that find no differences between the tinnitus group and a well-matched controlled group. So, I think the tool can be used to determine

correlates, but the studies have to be conducted well, and the controls need to be really made explicit.

- S1 28:15 Sure. So do you--
- S2 28:17 I think--
- S1 28:18 Go ahead.
- S2 28:19 Well, the only other thing I was going to say is that a good colleague of mine and I, we've submitted a sort of grant application to kind of look at this. And this is some of the research that I did in Nottingham, and I still need to work up some of the results-- is a really clean way of doing any sort of scientific investigation is a repeated measure of its design. So, it's the same person getting measured over and over again. And there, you'll see within that person what's happening. And so is the same correlate happening for your so-called tinnitus signal in that person? And how does that co-vary with things that you might do, like a hearing intervention, as I did with hearing aids? Or in the case that we want to investigate, my colleague and I, what happens from the early onset of tinnitus in the stages of early-onset into so-called chronification. So, if you sort of someone arbitrarily said, "This happens after six months or a few months of time," then if we follow people for a year or two, do we actually see changes in the brain networks with respect to-- in these individual people, and then as a group? Do we see common changes? So, I think that's a well-designed study and can inform us well, I think, about the sort of correlates.
- S1 29:50 About what might be tinnitus or what might be something else that's varying independent of tinnitus?
- S2 29:55 Yes, Yes.
- S1 29:56 And that was actually the question I was about to ask, or part of it, at least, was the next step. What can we look at next? And I was thinking of something a little different. Could we do a measurement of tinnitus distress in a population and then see how that correlates with different subgroups in the measurement and see what's - but it's the same kind of idea. What's changing, what's not, based on stratifying our group and differentiating on one factor or multiple factors as to what might be tinnitus, and what might be a cause or effect of tinnitus?
- S2 30:29 Yeah, absolutely.
- S1 30:31 So that kind of seems to be the next step in the research.
- S2 30:34 I think so. And as things start to reach more of a critical mass with respect to studies, then there will be more commonalities, not necessarily more differences. And I think that is being borne out, again from some of my colleague's resting-state fMRI studies, that she is finding sort of consistent results, sort of the resting activity of brain networks that differ between people who are distressed and not distressed with respect to their tinnitus and things like this.
- S1 31:05 So, with that, I'm just going to go ahead and recognize once again. We've been talking with Dr. Phillip Gander, who is an assistant research scientist at the University of Iowa. This has been a wonderful talk. Thanks so much for joining us here today.
- S2 31:18 Yeah, my pleasure. [music]
- S1 31:33 The American Tinnitus Association is a nonprofit organization dedicated to research, advocacy, education, and support for people who live with tinnitus. Gifts and

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