Hearing Health Hour Webinar Transcript
Hyperacusis | Monday, January 23, 5pm ET
Richard Salvi, Ph.D.

ANIL LALWANI - Well, welcome, everybody. We're going to be starting just shortly. Well, thank you for joining us today. Hello, and welcome to the "Hearing Health Hour" webinar. I'm Dr. Anil Lalwani, and I appreciate you joining Hearing Health Foundation for this "Hearing Health Hour" webinar today.

This event has a live captioner and is being recorded. You can enable closed captions by clicking the CC button located in the toolbar at the bottom of your screen. Now, if you need any other assistance using Zoom, just follow the link to the technical guide shared with the chat. Now, today's topic for the webinar is hyperacusis, a troublesome and potentially debilitating loudness intolerance disorder, a loudness intolerance disorder in which everyday sounds, regular sounds, are perceived as extremely loud, annoying, frightening, and, in some cases, just painful.

By way of introduction, my name is Dr. Anil Lalwani. I'm a professor and vice chair for Research in the Department of Otolaryngology-Head and Neck Surgery as well as associate dean for Student Research at the Columbia University's Vagelos College of Physicians and Surgeons in New York City. I'm also a board member at Hearing Health Foundation, where I oversee the Emerging Research Grants program, affectionately known as ERG. Now, ERG is a competitive program that awards funds to researchers conducting cutting-edge hearing and balance research. These grants supported many leaders in our fields. They support them to become leaders and successful scientists, including our illustrious speaker today.

Our presenter today is Richard Salvi, Ph.D., SUNY, S-U-N-Y, State University of New York Distinguished Professor in the Department of Communication Disorders and Sciences at the University at Buffalo and the director for its Center for Hearing and Deafness. Now, today, Professor Salvi will discuss developing behavioral animal models of hyperacusis and how these models help researchers investigate causes as well as future treatments. Now, we are proud to note that Professor Salvi was funded by ERG in 1978, '79, 1988, as well as 1990-1992. Now, the ERG program that provided seed money to scientists just starting out in their field of research is only possible through the generosity of supporters like you. If you'd like to support our work in hearing loss, tinnitus, and related conditions, you can do so today at hhf.org/donate.

We want to take a moment today, especially to acknowledge the work of the late Bryan Pollard who passed away last year. Now, Bryan [through Hyperacusis Research] did so much to advance knowledge of the condition. This organization brought together people living with hyperacusis, with clinicians and researchers working in the same area to better understand hyperacusis and advance both diagnosis and his treatment. He was instrumental in HHF's partnering with Hyperacusis Research Limited to fund dedicated hyperacusis grants through the ERG program. Now we'll move to Dr. Salvi's presentation. Please do ask your questions through the Q&A box linked at the, link is at the bottom of the screen, that we'll try to answer following the presentation. Dr. Salvi, take it away. We're so glad to have you today.

RICHARD SALVI - Well, thank you for inviting me to present here. I'd like to emphasize the importance of the early grants to young investigators. I actually had a grant as early as 1975 or '76 when I typed it up on my Smith Corona electric typewriter. And that grant was really instrumental in

getting my research career going. It gave me the courage to go forward and made me realize that some of the ideas I had were worthwhile.

Today, I'd like to talk to you about hyperacusis and when everyday sounds are too loud, annoying, and painful. I'm going to talk about some of the work we've done in this area. So to bring this home to you, hyperacusis, fundamentally, is this loudness intolerance disorder. To put this into perspective, normal speech sounds are normally around 60 to 70 dB, unless you're around somebody who really is a loud speaker.

But typically, when you're talking to colleagues, it's around 60 to 70 dB. When you go into the clinic, you can basically get your hearing tested for hyperacusis, or at least loudness hyperacusis, by measuring what's called Uncomfortable Loudness Levels. The audiologists would literally take the audiometer and keep raising the level of the sound or the noise until you said that's uncomfortably loud, and for most individuals, that's about 100 dB hearing level. For people with hyperacusis, these levels can be much, much lower.

This is a real person with severe hyperacusis. It's an individual that's 55 years old. He's a male, lives out in California as a financial adviser. And these are this person's Uncomfortable Loudness Levels. At this low frequency of 125 hertz, sounds of only 40 dB HL are too loud. And it becomes a little better up around 1,000 hertz. The level rises to 75 dB, and then it drops back to 65 dB. So sounds that were within the range of normal speech, somebody speaking loudly to this individual, he would find that way too loud.

People always ask, "How common is this? "I've never heard of anybody having hyperacusis." Well, it's more common than most of us would realize. It has a point prevalence of around 9%. So if you were to survey everyone, individuals in the country, you would find, at that moment in time, about 9% of the people would have some loudness intolerance disorders. Another question that often comes up is, "If you have tinnitus, "what's the chance of you having hyperacusis?" And the probability is as high as about 40%.

If you have ringing in your ear, if you're bothered by that, then it's fairly likely that you have hyperacusis. And these values could actually be higher than that because when you do the loudness tolerance test, a lot of people don't even realize they're sensitive to loud sounds. On the other hand, if you're a patient that has hyperacusis, then there's about an 86% chance, as high as 86%, that you'll have tinnitus. Tinnitus and hyperacusis seem to go together quite often, not 100% of the time, but very often.

As I mentioned, hyperacusis is linked to many, many disorders. We used to think, or people that work in the hearing field, we think of hyperacusis as only being associated with hearing loss, which indeed it is, but it's also associated with migraine. So if you have migraine headaches, very likely that you're going to suffer from hyperacusis. People that are under a lot of stress often develop tinnitus and hyperacusis.

Stress, something we'll come back to in my talk, is also a factor. In many call centers, people develop what's called acoustic shock syndrome. People that work in these call centers pick up a phone, there'll be a large click on the other end of the line. And then when they do that for a long time, they develop this acoustic shock, where the sound actually feels painful to the ear.

Autism, people that have autism, have sensory hypersensitivity disorder. They don't like to be touched, lights are bothersome, sounds are bothersome. This is very common. Williams syndrome is a genetic disorder. Lyme disease is common to get tinnitus and hyperacusis. My sister-in-law developed Lyme disease, and she had some facial paralysis, which is associated with tinnitus and

hyperacusis. Ménière's disease disease is a hearing disorder that also causes balance disorders. It's unusual in the sense it has a low-frequency hearing loss associated with it.

And my wife just developed Ménière's disease about five or 10 years ago. And when her Ménière's disease is kicking in, when I take the dishes out of the dishwasher, she tells me I'm slamming the dishes around. So I have to walk away and get out of the room so I don't bother her. Lupus is another disorder, autoimmune disease. Tay-Sachs... Tay-Sachs is another disorder. It's a lysosomal storage disease. And this list could go on maybe twice as, three times as long. So hyperacusis is very common in many other disorders.

There was a review done by some researchers probably about eight or nine years ago by Tyler, Pienkowski, and some other individuals that came up with four categories of hyperacusis. The two I'm going to talk about today are loudness hyperacusis, this is when sounds are just way too loud. Another one that's associated with loudness hyperacusis is avoidance hyperacusis. You don't want to be around sounds. You purposely get out of the way when loud sounds come up. Another one is fear hyperacusis, when you hear loud sounds, and it invokes fear. And the last one on the list over here is pain hyperacusis, where, when sounds are too loud, you actually feel pain, usually around your ear and your face.

We've developed models, animal models, for the first two. And one of the reasons we did this is the lack of animal models really hinders research on trying to understand the basic biology of what causes hyperacusis. We typically use a rat in our animal models. One of the big questions is: How do you measure loudness hyperacusis? Or how do you measure loudness in an animal? You can't ask the animal to tell you when it's too loud, so you have to develop some behavioral techniques for doing this. And we read the literature, and we found that in the human literature, if you measure reaction time to sounds of various intensities, you'll find that sounds that are very low intensities, you respond slowly to them, and as the intensity increases, you respond more quickly. And so we use this technique to measure loudness growth, both in humans as well as animals.

The way you do this in an animal model is pretty simple. You take a rat and you food-restrict the rat. The rat gets fed once a day. And when you're feeding the rat, the rat sits in a chamber over here, and he can get a food reward if he sticks his nose in the nose poke hole over here. And he's got to put his nose in here and hold it there until he hears the sound. And when he hears the sound, he's supposed to pull his nose out, and if he pulls it out in two seconds, he'll get a food reward over here in this food dispenser. We measure the time between when we present the sound, in this case, a broadband noise, and when the animal pulls its nose out of the nose poke hole over here. And these times are very short. They're on the order of milliseconds.

This is the response latency over here. You can see that at a low sound level, 30 dB sound pressure level, the rat takes about 225 milliseconds to respond. And as we begin to increase the sound level, you can see there's an orderly decrease in the reaction time over here. We can measure in each individual animal the reaction time versus intensity functions. Each animal is a little bit different, so you have to measure a baseline measurement before you do any measurements of hyperacusis.

One of the big challenges in addition to developing an animal model was, how can you reliably induce hyperacusis? We, again, went back, read the literature very closely, noting that tinnitus and hyperacusis are closely related, and we used a drug called sodium salicylate, a high dose of this drug. Sodium salicylate is the active ingredient in aspirin, and if you take a really high dose of this, it'll induce tinnitus in humans as well as animals. The research on this basically came out of the studies on rheumatoid arthritis.

Aspirin used to be a treatment for rheumatoid arthritis. Doctors would tell their patients, "Keep increasing your dose of aspirin "until your ears start to ring, "and then lower the dose, "and that's the dose to treat your rheumatoid arthritis." So we said, let's try to give high doses of aspirin to see how it affects the reaction time versus sound intensity functions. The first thing we did is we measured the baseline reaction time intensity function before we gave the drug in a group of rats. This is the blue line over here, and you can see the orderly decrease in reaction time as intensity increase.

And then, we took the rats, gave them a high dose of sodium salicylate, and measured the reaction time. And you can see here at these high intensities, the reaction times are much faster, much shorter than they were before we gave the drug. We take this as behavioral evidence that this is louder than normal and the animal has developed hyperacusis. The only thing that's unusual about this graph is the reaction times at low intensities are a little bit longer, and the reason for this is this drug salicylate also gives you a hearing loss. These sounds here, after we give the salicylate, is barely audible.

Now we have a really cool way of reliably inducing hyperacusis in an animal model. So as I mentioned in the beginning of my talk, chronic stress has been implicated in hyperacusis and tinnitus. And what stress does, it disrupts your endocrine system, the hypothalamic-pituitary adrenal axis. This is a structure that's, part of it's located right under your eyeballs in the pituitary, in the gland. So one of the things we wanted to do is go back to our salicylate model and see whether this induced stress. One of the ways you can do this is measure a stress hormone called corticosterone. And what we did is we took the rats and we gave them varying doses of sodium salicylate, including high doses, and we measured the amount of stress hormone in the animal. So we take a blood sample from the animal, and then we take that out, and we measure how much corticosterone.

If we don't give any salicylate, the stress hormones are very low. If we give 50 milligrams per kilogram of salicylate, they remain very low, but as soon as we get up to 150 or 250 milligrams per kilogram, you can see the stress hormones start skyrocketing. And what's interesting about this graph is the 150, 250 milligram per kilogram dose, these are the same doses that you need to induce tinnitus, and these are the doses that you need to induce hyperacusis.

This prompted us to think of other experiments, and one of them was, does chronic pharmacological treatment with stress hormones cause hyperacusis? Does stress all by itself, is this enough to do it? We took some rats, in their water, we put 225 micrograms of, of corticosterone per milliliter in the water, and we fed it to them for 28 days, okay? And then before we gave the drug, we measured their hyperacusis. And then afterwards, we also made some electrophysiological measures, okay?

The rats were given the corticosterones. Here's our reaction time intensity function. We can measure the response latencies. This is the sound intensities. Before we give the drug, you can see the reaction times are relatively long. They get shorter as we increase the intensity. But after the animal's been on the corticosterone for a few weeks, you can see the reaction times are much, much shorter than normal. We believe that this drug corticosterone is maybe a key factor in inducing hyperacusis in some individuals. The next thing we wanted to do is, what does this corticosterone treatment do to the nervous system of the rats? Does it affect the inner ear, or does it affect the brain, or does it affect both structures?

The way we went about doing this is we made some measurements of an electrical potential you can record from the inner ear. It's called the CAP, which stands for compound action potential. It measures the neural output of the inner ear, the gross neural output. The CAP is measured over

here in microvolts. This is the sound level. The blue lines show you the results before we gave the drug. As we increase the intensity, the neural response of the cochlea increases, goes up. Do the same experiment, but now do it in a group of rats that have been treated with corticosterone for three to four weeks. You can see that there's absolutely no change in the response.

These data show us that this corticosterone is not affecting the inner ear, at least in the measurements that we can make, but it's probably having an effect somewhere in the central nervous system. In order to test the effects on the central nervous system, seeing if corticosterone affects the auditory cortex response, what we did is we put some electrodes, implanted them right over the auditory cortex in a rat. This allowed us to monitor the measurements over time. This shows you the electrical activity, the amplitude in microvolts, as a function of time over here. And what we're doing, we're playing an 8 kilohertz tone, presenting it at 90 dB, and the sound comes on here at 0 milliseconds. We don't get much of a response here in the beginning of the, when the sound first comes on, but around 7 to 15 milliseconds, we see the response over here. The black line is the response before we gave the drug corticosterone to the rat. You can see there's a nice response, consistent response.

But interestingly, after we give the corticosterone, we see a huge increase in the response. And this huge increase occurs between about 6 and 17 milliseconds. This latency of the response corresponds well to where the time delayed to getting the signal to the auditory cortex. This corticosterone is not affecting the inner ear, but it's having a dramatic effect on the cortex. You can develop a model of hyperacusis. And this model applies not only for the corticosterone stress hormone. We've seen the same results with salicylate and with intense noise exposures. What we think the hyperacusis originates in is an amplification of the neural activity as it's going from the inner ear to the brain. So here, we're plotting the neural output as a function of sound input. In the normal system, you have a normal gain, you have this straight line. As the sound level goes up, the neural activity increases, but in cases where you've induced hyperacusis, we see if the activity goes up much greater than it normally would. There's an increase in the gain and amplification of the system. Things are just too loud when the sounds reach the brain.

Who are some of the people that develop hyperacusis and tinnitus? Well, if you look at some of the data from combat personnel, military personnel, these individuals are exposed to intense noise, and if you're in combat, you're under a tremendous amount of stress. So one of the things we wanted to do is, if you're under a lot of stress, noise stress, what does this do to your stress hormones? These are some data that came from 1963 by an investigator, Henkin. They took some rats, put them in 130 dB noise, 220 hertz, this is very low-frequency noise, and they looked, took out the adrenal glands, and they looked at how much corticosterone stress hormones was being released from these rats. And you can see during the noise exposure, the corticosterone stress hormones were extremely high compared to the control rats. So that was one experiment.

Another experiment came from a guy by the name of Samson, 2007. He did something a little bit different. They took some rats, exposed them to 100 dB noise for four hours per day, but they did this for 1 day, 15 days, and 30 days. And after the animals would come out of the noise, they would get a blood sample and measure the corticosterone stress hormones. And you could see that the levels in controls were much lower than the animals that were noise-exposed. So we think one of the factors that could be important for hyperacusis is just stress, can be induced by different types of stress. Noise is one of the factors. So, does intense noise exposure induce stress? Or does it induce hyperacusis? So what we did is we took some rats, put them in a very long-duration noise exposure. So they were stressed for a long period of time. We had 104 dB noise. The noise was high frequencies between 16 and 20 kilohertz, and they were in the noise for 12 weeks. And then we took the animals out of the noise, and we wanted to assess their hearing, and we wanted

to see whether they have hyperacusis. This shows you the amount of hearing loss that the animals had. The animals had a high-frequency hearing loss. Most of the hearing loss was confined to between 20 and 24 kilohertz and a mild hearing loss at 16 kilohertz and completely normal hearing at the low frequencies. Afterwards, we tested their hyperacusis at frequencies down here, and we found that they had hyperacusis.

I'll show you the next data on the reaction times. This is our reaction time measure of loudness. This is sound pressure level. These were the reaction times of the rats before we gave them the noise exposure. These were the reaction times after we gave them the noise exposure. You can see the reaction times actually became a little bit longer at the low sound levels because they have a hearing loss here, and things don't sound as loud due to the hearing loss. But as the sound intensity increases, you can see the reaction times get much shorter, significantly shorter than normal. We saw this at 4 kilohertz, 8 kilohertz, and 16 kilohertz. At 4 and 8 kilohertz, the animals had no evidence of hearing loss whatsoever.

Another thing I mentioned to you is, do rats, do they avoid loud sounds, or are they fearful of loud sounds? Can we develop a test of that? One of the investigators of my lab, Manohar, basically developed this technique. What he did is he had two sound chambers or two chambers, one a dark sound booth with a loud speaker built into it. The animals could leave this dark room, go down the runway and go into an open arena over here where there's bright lights. Rats have a natural aversion to bright, open spaces.

If you take the rats, a normal rat, put them in this open arena, they go back and hide out in the dark box over here. They spend about 90, 95% of the time in the dark box. What we did is, we said, is the noise that we play to them, will they avoid it? We turn the sound on, we put a noise in here, turn it on, and we increase the intensity, and see if the rat will leave the booth over here and go to the open arena. So when it's quiet in this dark booth, they spend about 95% of the time in the dark room. Soon as we start turning the noise up, 60 dB, they go into the open arena over here about 20% of the time. And then when it gets up to 90 dB, they spend more time in the open arena, and they only spend about 60% of the time in the dark box. You can measure their avoidance. They're avoiding the sound in this dark box over here.

What happens when we basically give the animals a high-frequency, noise-induced hearing loss? So does this prolonged noise-induced hearing loss cause sound avoidance? So here's the percent of time the rats spent in the dark. This is the control group, spent about 95% in the dark and quiet. When the noise is 60 dB, they spend about 85%. When the noise is 90 dB, they spend about 80%. In animals that have been given this high-frequency hearing loss, when we test them with a low-frequency noise that only goes from 2 to 8 kilohertz, where their hearing is normal, what we find is, as we jack up the sound level, the rats get out of the dark box and they go into the open arena. They're avoiding the sound in the dark box over here. There's a significant reduction over here.

Now we have two nice tools for measuring hyperacusis, loudness hyperacusis in one case and avoidance hyperacusis in another case. What about chronic stress? People have done studies in humans showing that chronic stress disrupts the hypothalamic pituitary axis, the HPA axis. And one of the persons that did some of the really seminal work on this is Sylvie Hebert from Montreal. And what they did to test the sound of stress was to have people give a speech. And what they found is when these people had severe tinnitus or severe hyperacusis, then they had what's called a blunted cortisol response, a blunted stress response to psychosocial stress.

Here's her study. What they did is they measured samples of cortisol from their human subjects, and they collect the samples before they gave the speech, during the speech, right after the speech, and then for 60 minutes afterwards. And these are the normal subjects. Just after they

give the speech, just after they test them, get a blood sample from them, they see a huge spike in their stress hormones, and about an hour later, they go back to baseline. But when they tested their patients that had tinnitus and hyperacusis, they found they got a blunted stress response, indicating that this HPA axis was probably disrupted in their patients. And they've shown this several different times.

We thought, let's see if we can replicate that human study in our rat animal models. We did this with the prolonged noise exposure that I told you about. What we did with our rats is we took a sample of their blood before they were stressed. And this is the control group, this is the noise exposure group. There's no difference in their pre-stress baseline cortisol measures. The way we stress the rats, we put them in a restraining device for about 30 minutes. They don't like being in there, they're unhappy about that. And then afterwards, we basically measure their stress hormone levels. The control group, you see a huge increase. Their HPA axis is normal. The values go up, way up. But in the group that was noise-exposed, their stress hormone levels are reduced. They show a blunted stress response pretty much like Sylvie Hebert's study in humans.

This is really a nice demonstration of how you can disrupt the HPA axis with a long-duration noise exposure in rats, an exposure that will induce hyperacusis. I'm going to change topics on you now, bring you back into the human-animal domain. I mentioned earlier that people with autism or autism spectrum disorder oftentimes have sensory hypersensitivity disorders, including hyperacusis.

One of the leading causes of autism in humans is Fragile X syndrome. It's a cause of autism spectrum disorder. What we did is, Ben Auerbach, one of the faculty members that work with me, found a Fragile X rat that had this deficiency. That's an FMR1 gene which lacks the protein FMR1 protein. And what we did is we took these rats and we tested them for hyperacusis in our animal models. This has been published about a year ago. The first thing we did with these rats, the FMR1 knockout rats, is we wanted to see if they had normal hearing. This is the threshold for hearing. This is frequency. These are the normal rats, normal wild type rats, the black lines. These are the rats that have the Fragile X deficiency, FMR1. They have normal hearing.

There's no difference in hearing thresholds between the two groups. What is different about them, however, is, once you get above threshold, you find that the rats that have, the FMR1 knockout rats have hyperacusis. So here, we've measured the reaction time. Here's the sound intensity. This is the group of rats that are wild type, or normal rats. This is their reaction time intensity functions. And this is the group, FMR1 knockout rats, that we think have hyperacusis and we think have autism. You can see that their reaction times are much, much shorter than normal, are shorter than the control group over here. There's no difference at threshold, but as soon as the sound becomes audible, the FMR1 rats think it's louder than normal.

One of the really important questions about many disease states, including hyperacusis, is, why do some individuals develop tinnitus? Why do some of them develop hyperacusis? I've shown you a bunch of data that suggests that chronic stress may disrupt the HPA axis in certain individuals. And could genetic factors play a role? And there's some human and animal data that suggests this.

Let me show you a piece of speculation on my part. This is HPA axis in a genetically anxious mouse. These mice, these genetically anxious mice, have been genetically developed. They are very anxious mice. This group over here, McGill, 2006, in the Proceedings of the National Academy of Sciences, they measured their cortisol levels before they were tested over here and during restraint stress. You can see the corticosterone levels, when the animals are being stressed. This is the normal mice. You can see the stress response over here. The corticosterone

levels rise. But in the animals that are genetically anxious, you get this significantly larger increase in the stress hormones. These animals basically have a very strong stress response.

And the speculation on my part is, if these animals are anxious and you repeatedly stress them, day after day after day, eventually, this stress response is going to burn out, and they're going to develop a blunted stress response. This is total speculation on my part, but this gives you some idea of some of the genetic factors that may be involved.

So I think I'll stop here. I'd be happy to take some questions from the audience.

ANIL LALWANI - Professor Salvi, that was a wonderful, wonderful talk and an amazing body of work about a very, very hard area. And it's amazing that you have an animal model that allows you to investigate it. There's several questions that we have from, that are kind of generic from several individuals. One is, what are the different types of hyperacusis and how are they distinguished from one another? Can you speak about that a little bit?

RICHARD SALVI - Sure, I put together a slide that might help to do this. This is really a Venn diagram. You can sort of see the circle here in yellow. That's loudness hyperacusis. That basically encapsulates many of the other types of hyperacusis. So if you have loudness hyperacusis, you may have a fear of sound. So that fear part of the circle over here largely falls within the loudness category over here. Although, you could have fears that are not associated with loudness. Same with annoyance. You could be annoyed by sounds. Some people have, don't like chewing food, for example, but the sound is not loud, it's just bothersome. So they could be annoyed by that. The other category is pain hyperacusis, and this one's totally enclosed within the loudness of the Venn diagram over here. Play a loud sound, and some individuals, they get just tremendous pain in their ear, their face, and these areas over here. And we don't actually know exactly what causes that. I have a slide later that will address that issue.

ANIL LALWANI - And one of the other questions that several of the attendees also wanted to know about is, what is the difference between recruitment and hyperacusis?

RICHARD SALVI - Yeah. I thought I'd put a slide in here that can explain the two. Loudness recruitment is very common. If you have a sensory neural hearing loss, you're very likely are going to have loudness recruitment, not necessarily hyperacusis. This graph over here is a illustration of the differences between the two. On the y-axis over here is loudness. It's measured in a psychological unit called a sone of loudness. This is sound intensity. This is a normal individual, the black dashed line over here. This is somebody that has loudness recruitment. Loudness recruitment is usually associated with hearing loss. So you can't measure anything till you get up to the threshold of hearing. But once you do, once you reach the threshold of hearing, loudness grows very rapidly. It catches up to the normal loudness growth function, and then follows it, doesn't go above the line. But if you have hyperacusis and a little bit of hearing loss, what happens is loudness grows very rapidly, catches up with the normal loudness growth function and eventually exceeds it. Things become too loud. In this example here, a sound of around 80 dB is just as loud as a sound that would be maybe 100, 120 dB. There's a clear difference between loudness recruitment and hyperacusis.

ANIL LALWANI - Got it. And based on some questions that were submitted before, as well as during our question Q&A box, now, can you discuss the pain hyperacusis in more detail?

RICHARD SALVI - Sure. Maybe 10 or 15 years ago, we started to do studies of tinnitus. And one of the things we found is on maybe 70% of the people that had tinnitus, they could modulate their tinnitus by moving their head, shoulders, and eyes. And when we did try to correlate this with nerves, we found that many of these nerves were associated with the cranial nerve VII, upper cervical nerves in the shoulder area over here, the vagus nerve, cranial nerve, the trigeminal nerve, which is one that innervates your face, and the glossopharyngeal nerves. All of these nerves seem to be associated with tinnitus, and many of the patients that get pain hyperacusis, they get pain in areas that are associated with these nerves.

There's one other type of pain hyperacusis that's been developed from animal models on, thought to involve the Type II auditory neurons. These are the neurons that basically hook up to the outer hair cells. The outer hair cells are sensory cells in your inner ear. They're often the first sensory cells to be damaged by loud sounds. And when these loud sounds come in, they seem like these sounds are, can activate the Type II auditory nerve fibers that connect to the outer hair cells. So, there are kind of two models, one a cochlear model involving the Type II auditory nerve fibers and another model involving cranial nerves and nerves that innervate the face and upper cervical areas. These are thought to be involved with pain hyperacusis. We know very little about that right now.

ANIL LALWANI - Along those lines, the pain sensation, is that coming from the inner ear or is it coming from the brain? Where is that pain sensation coming from?

RICHARD SALVI - I don't think people really know the answer to that, but one hint about where the pain is coming from is phantom limb pain. Patients will get a limb cut off, the limb is no longer present, but when you touch the stump, the person will complain of pain from the missing limb. So many people think that pain could involve the central nervous system, pain systems and the central nervous system that are disrupted. And so that would fit in with some of these other models over here, like the cranial nerves that I mentioned. I think you need to turn on your audio, Anil.

ANIL LALWANI - Sorry about that. One of the questions that everybody's asking is, are there effective treatments and how can they get them? What's out there for them, the people that are suffering from this?

RICHARD SALVI - Actually, there are things that you can do. They're not publicized as well as they should be. But when I started to do this work, many patients would call me up, and our clinic at the University at Buffalo developed a tinnitus and hyperacusis clinic. There's other clinics like this and Rich Tyler's center at the University of Iowa. But these therapies basically involve presenting moderate-intensity sounds or low-intensity sounds along with counseling and education. And the idea here is these moderate-intensity sounds... Let me back up one step. Hyperacusis often

develops because you have a peripheral hearing loss. When you have a peripheral hearing loss, you reduce the flow of information into your auditory brain. Your auditory brain tries to compensate for this by turning up its volume control. And a good analogy for this is when you're listening to the radio and you drive out of range, the signal weakens, and you reach over to your dashboard on your car and you turn up the volume control, and then when the signal comes in, wham, it gets way too loud. The idea of the sound therapies is, by putting low-level sounds in, a lot of the time, you can get the auditory system to turn down its volume control. This also involves some counseling and some education for the patient.

And when I talk to our clinicians that have done this for 10 or 15 years, they tell me that when they have tinnitus and hyperacusis patients come in and they go through these therapies for a period of maybe six months or a year, their hyperacusis is the first thing to go away and the tinnitus becomes less bothersome. The thing that most patients want is an instant cure. There are no drugs that we're aware of that will instantly turn off your tinnitus or your hyperacusis. But the things that seem to work or ameliorate the symptoms in a large portion of the population, maybe 50 to 60%, would be the sound therapies involved and counseling in hyperacusis. And there's a fair amount of clinical data to support this. The problem group is the 5, 10, or 15% where the sound therapies and counselings just don't seem to work. In some cases, the sound actually makes it worse.

ANIL LALWANI - Does... Is there hyperacusis in children? Is it different than adults? And along the same lines, there are a few questions about, you know, you alluded to different causes of hyperacusis, is hyperacusis experienced differently depending on the cause of the hyperacusis in the first place?

RICHARD SALVI - Well, the questions you're asking are extremely difficult. I work with animals. I don't have all the answers for this. I suspect that each person that walks in with tinnitus and hyperacusis, it might be a little bit different in terms of the cause and in terms of what it sounds like to some individuals and the degree of impairment. You know, some people, very low-level sounds are bothersome. Other people, you have to raise the level up to maybe 80, 90 dB. So there's probably large individual differences and differences in the way they're experienced.

I mentioned that my wife has hyperacusis, and one of the things I've noticed about her is that sounds that have like a sudden onset, clanking of a pan or a dish, that really sets her off, whereas noises that are more steady-state are less bothersome. And we've seen some of this in our Fragile X model with our animal models, where the temporal integration of loudness seems to be disrupted. So...

ANIL LALWANI - Any relationship between dizziness and hyperacusis? There's a few questions about those, possibly even in Ménière's disease.

RICHARD SALVI - For sure. My wife is an example of this. It seems, she'll tell me, around five or six o'clock every day, she'll start feeling a little dizzy, she'll start getting tinnitus, she'll start getting hyperacusis. And she has what we think is Ménière's disease. Ménière's disease is a disorder by exclusion, to a large extent. We don't have really good biomarkers for it. But she has the low-

frequency hearing loss that fluctuates. This may be associated also with some other disorders, like maybe migraine and fibromyalgias. Maybe you can answer the question for me. Is migraine associated with dizziness? I think it is, yes.

ANIL LALWANI - Yes.

RICHARD SALVI - Yeah.

ANIL LALWANI - You know, one of the other questions has to do with... You alluded to the phantom limb, some relation between tinnitus and hyperacusis. So is this... And associated between stress and corticosterones and so on. So should one try to treat the ear or the brain, or both? What are your thoughts about that in terms of interventions?

RICHARD SALVI - Well, I mentioned the sound therapy, but it's not just sound therapy. There's many clinicians that think the, the counseling and education are as important or maybe more important than the sound therapy itself. Oftentimes, our brain gets into a loop. For example, if you have tinnitus, many tinnitus patients will keep a daily record of when they get their tinnitus. So they're constantly listening for their tinnitus. People that usually are successful in therapies, they basically say, "We try to just ignore the sound that's there, "and it doesn't bother us anymore." So the annoyance part of this, trying to control it, maybe from the counseling aspect, seems like it's critically important for some individuals.

ANIL LALWANI - Is there a test for hyperacusis? We had questions about recruitment versus hyperacusis, tinnitus and hyperacusis, so on. You have wonderful tests for your animal models, of course. I'm wondering, is there, if somebody comes to me in my practice and says, "I'm sensitive to noise," and if I want to differentiate recruitment from hyperacusis, would that be basically a subjective thing based on what they tell me, or is there a test for it, in your mind? Or are you working on a test for it?

RICHARD SALVI - I am working on a test for this. The reaction time measures that we use, one could imagine developing age-related reaction time intensity functions and see if people fall way outside the normal range. There are other tests that you can use, the Uncomfortable Loudness Level. If somebody comes in, like in the second or third slide that I showed you, the individual that had Uncomfortable Loudness Levels around 50 dB or so, person for sure probably has at least loudness hyperacusis there. There are other tests, there are other paper and pencil tests that are used to measure hyperacusis. There are several of them that are out there, hyperacusis questionnaires. And the third thing is just-

ANIL LALWANI- Go ahead.

RICHARD SALVI - Loudness scaling. There's a woman, Jennifer Melcher, that published some really nice papers, where she measured loudness scaling measures in individuals with tinnitus, and found that many tinnitus patients were unaware that they were intolerant of loud sounds.

ANIL LALWANI - As we're down to our one or two minutes, we have sort of a broad question for you with unfortunately a very short time period. What do you think are the areas we should be focusing on, and how do we get more people interested in this research?

RICHARD SALVI - Well, there are a lot of powerful tools that we have now to investigate hyperacusis. One of the things that I got involved with in my non-animal work is brain imaging. Some of the work that's been done on Williams syndrome, for example, they did some functional MRI, where you can actually look inside the brain and see what areas get turned on when you play loud sounds. And those could give us really important clues in human subjects on basically what structures might be involved in hyperacusis and how we might clinically treat them. So brain imaging in human subjects, I think, has some wonderful opportunities.

The animal models, I think, that we developed will also give researchers some tools that they can use to do electrophysiological or neuroanatomical studies in animal models. You can't... If you know that an animal has hyperacusis, now you can begin looking at the electrophysiological correlates for it or the neurochemical correlates for that. But unless you have the models, unless the animal can tell you, "I'm really bothered by this loud sound," you're really stuck. So those are areas I think people could capitalize on the work that's been done that I've presented here.

ANIL LALWANI - Well, Dr. Salvi, thank you so much for this incredibly informative presentation. I also want to thank all the attendees. We are so grateful to you, our community, for your support of our Emerging Research Grants program. Remember that you can donate to our efforts to advance better treatments and cures for hearing and balance conditions by going to HHF, Hearing Health Foundation, hhf.org/donate. Thank you again for joining us, and please enjoy the rest of your day.