Hearing Health Hour: Revealing Hidden Hearing Loss
Date: April 25, 2022
Presenter: Sharon Kujawa, Ph.D., with moderator Anil Lalwani, M.D.

ANIL LALWANI - Hello, and welcome to our Hearing Health Hour webinar. We thank you for joining us for another research presentation from the Hearing Health Foundation. Today's topic is one that has been in the mainstream news, that of hidden hearing loss, where patients present with difficulty hearing, especially in the presence of noise, but the hearing test is normal. Now, our audience should not confuse this with hearing loss that is hidden by the patient because of concerns as to what their friends or society may think if they were to wear hearing aids.

This event has a live captioner. It is being recorded. You can enable the closed captions by clicking the CC button in the toolbar at the bottom of your screen. If you need any other assistance using Zoom, follow the link to the technical guide shared in the chat.

By way of introduction, my name is Dr. Anil Lalwani I am the professor and vice chairman for research in the Department of Otolaryngology–Head Neck Surgery, as well as the associate dean for student research at Columbia Vagelos College of Physicians and Surgeons in New York City. I'm also a board member of the Hearing Health Foundation, where I oversee the Emerging Research Grants program, also affectionately known as ERG. ERG provides critical funds to researchers, especially early in their career, who are studying hearing and balance conditions. These grants have supported many leaders in our field to become successful scientists, including our illustrious speaker today.

This ERG program is only possible through the generosity of supporters like you. Now if you'd like to support our work on hearing loss, tinnitus or related conditions, you can do so today at hhf.org/donate.

Today we are thrilled to have as our presenter, Dr. Sharon Kujawa. Dr. Kujawa is a professor of otolaryngology- head and neck surgery at Harvard Medical School, where she's also the director of audiology and serves as a principal investigator at Mass Eye and Ear. Her research focuses on primary causes of hearing loss, like noise exposure and aging, aiming to reveal the underlying cellular damage and its consequence to hearing function.

In recent years, this work has given rise to the concept of hidden hearing loss. It's the declines in hearing function that is not revealed by the standard hearing test, but is

nonetheless experienced by the individual who suffers from it. Dr. Kujawa will shed light on this enigmatic condition that she and her colleagues have done so much to elucidate.

Dr. Kujawa is a 1999 Emerging Research Grant recipient, a fact that we're so proud of. In addition, she's a member of HHF's Council of Scientific Trustees, as well as our newest member of the Hearing Health Foundation's board of directors. That could go on forever, but that would only take time away from Dr. Kujawa So we're so pleased to have Dr. Kujawa here today and to hear her talk about revealing hidden hearing loss. Now, please do ask your questions through the Q&A box linked at the bottom of the screen. We're going to try to answer all the questions we can at the end of the presentation. Dr. Kujawa, we're so excited to have you here today.

SHARON KUJAWA - Okay, thanks very much for that really kind introduction, and seriously, thank you for the invitation by Hearing Health Foundation to share this information with you. It's been mentioned that I was an early awardee of one of these foundation grants. I was a newly minted assistant professor at the University of Washington when I received this support. And at the time, I was really focused on looking at clinical diagnostic measures for Ménière's disease. It was presenting some very significant challenges in the clinical setting.

Today, our work really focuses on other forms of acquired sensorineural hearing loss in humans, but the focus on improving clinical diagnostic measures of really forming the information base that allows us to address cellular-based diagnosis that will be increasingly important as clinical trials for sensorineural hearing loss come on line. So I see this work as kind of an ongoing process of the research program that was very generously funded by Hearing Health Foundation at its earliest stages.

What I'm going to do today is take you through some of the focus of the work that we've done. Some of this will be review for those of you who have heard parts of this story before, but I think it's important to put a framework on the studies. Basically, this image of the structures of the outer, middle, and inner ear should be familiar to many of you.

I'm going to be focusing my attention here today on the cochlea of the inner ear. I do that because the cellular subtypes that are contained within that organ are those that are critical for me to describe the cell types that are involved in different injuries, contributing to sensorineural hearing loss in general, and the concept of hidden hearing loss that has been discussed in particular.

Within this spiral shaped structure is an organ of Corti. This schematic here basically shows several of the major cell types that we are interested in. Outer hair cells here shown in red are really remarkable hair cell subtype that provide an amplification of low level signals and allow us to really hear very low level pressure changes in the inner ear, in the cochlea of the inner ear. The inner hair cells in this system are really the traditional sensory transducers.

These are the cells that are well connected to the auditory nerve fibers that then leave the organ of Corti and move toward the brain.

These cochlear nerve fibers carry these signals that have been shaped by outer ear, middle ear structures, then by the outer hair cells, and transduced by the inner hair cells to form a signal that is appropriate for the auditory nerve. That communication takes place through synapses. These are structures that allow information flow from the inner hair cell to the auditory nerve fiber.

I'm going to be talking a lot about those synapses today. Here again is the schematic of the organ of Corti. This of course is image of a real organ of Corti in a cochlea. Here, you can see the fluid spaces, you can see the rows of outer and inner hair cell stereocilia here that run the length of structure. If we zoom in a little bit more, you can see the really remarkable architecture of this organ in the normal situation.

We have outer hair cells here. Again, these red guys down here that are shaping the signal that is then delivered to the inner hair cell here. And so in health, these structures allow us to have remarkable sensitivity and frequency selectivity to signals that are incoming to the cochlea.
I'm going to use the case of noise exposure here to show how these structures, which allow us to have such incredible sensitivity in the normal condition, can be altered if sound, for example, is presented at a level that is well above the threshold sensitivity. So here, you can see, almost in real time, changes in the outer hair cell structure of the cochlea, which then correspondingly are reflected in threshold sensitivity of an individual who had been exposed to a great deal of noise during their lifetime.

This is an individual who has a high tone sensorineural hearing loss. We know from their history that they had a good deal of noise exposure in life. This individual generously donated their temporal bones for study. When we look at the structures within this organ of Corti, what we see is a very large loss of outer hair cells here in the region that is reflected in this reduction in threshold sensitivity for this individual. Threshold elevations and outer hair cell loss are paired in this particular case to show you really an overt form of sensorineural hearing loss that we can easily identify on the clinical audiogram. Not all exposures, of course, can result in permanent threshold elevations or in frank outer hair cell loss.

I'm going to be spending a fair amount of time this afternoon, talking about that latter case. The press, I think, has probably focused a good deal on the term hidden hearing loss. Dr. Lalwani talked a bit about what we refer to in this case. There have been a number of definitions of hidden hearing loss that have basically been put forward. When I talk about it here in this presentation, I'll be referring it back to injury in the cochlea that is not really reflected in the clinical audiogram or the audiogram that we obtain in laboratory settings as well.

It is not really easily seen in the traditional ways that we have studied cellular losses by histologic procedures in the cochlea. You can see here some of the forms, the etiologies of sensorineural hearing loss that is acquired by individuals, by aging, by noise exposure here of many different types. In some cases, by ototoxic drugs that may be given as cancer chemotherapeutics. In each of these cases, there can be not only the hidden hearing loss that I'll be talking about, but also overt hearing loss that sometimes is reflected in the clinical audiogram.

I had the opportunity to be involved in a study a number of years back when I was at the University of Washington, that basically looked at thresholds of men who had been noise-exposed during their working lifetime, and then had been tested longitudinally as part of the Framingham Heart Study cohort. And those studies hinted at the notion that individuals with that kind of noise exposure history actually had hearing that aged differently from those that did not have that kind of exposure during their working lifetime. As you can imagine, sorting that out in humans retrospectively with a study that really wasn't designed to answer that question in the beginning resulted in a lot of hand wringing, but I thought that it was a question that I could address in a more straightforward way. It was certainly a question that I was interested in.

There was a great deal of thought that the notion that a noise exposure was a time-limited event. You would see a result from a noise exposure. The noise would stop. The ear would undergo some amount of recovery, depending on how intense or how damaging the noise exposure had been. And then at really longer post-exposure times, there really was the thought that noise did not continue to change the way that ear aged going forward. So we decided to test that hypothesis, and when we did that, we had a very unexpected finding, and that is that those vulnerable hair cells were not really the most important change that we saw in these ears.
What we saw was something that I'm going to try and describe for you next. In the studies that we did, we created a noise exposure that produced temporary changes in threshold sensitivity. You can see those depicted here on these graphs. On the left-hand side are elevations in threshold that is reductions in the sensitivity to low level sound that are reflecting the outer hair cell contributions to that response. On the right, we're looking more at the neural response to those signals. What we see is that one day after a noise exposure, and this band just gives you an idea of the frequency content of that band of noise.

I should let you know, for those of you who are not familiar with these graphs, basically, we have frequency or the pitch of the tone along this bottom axis here from low to high. Then on the side of the graph is depicted the amount of change in the threshold sensitivity after the noise. So before noise is given as zero, and then one day after the noise, you can see it took a greater level of sound to be able to just detect these signals. With time, the thresholds got better and returned back to baseline. And that was reflected in both the hair cell and the

neural responses. And that's something that many people had reported previously. There can be temporary changes in sensitivity that are seen after a noise exposure. If the exposure is not too damaging, the thresholds can return to normal.

But what we observed in not just threshold sensitivity, but if you follow the response to higher levels, you see that those outer hair cell-based responses came back to normal. So here in the red is how they were reduced at one day after exposure, but by a number of weeks after exposure, they're really not different from responses of ears that had never been exposed to noise. In contrast to that, you see this very dramatic reduction in the neural response.

This is activity of the auditory nerve fibers that is being reflected in these response properties here. Again, a big shift one day after exposure, but even eight weeks after the exposure, there is this dramatic reduction in the magnitude of this neural response. So looking at the ears of animals that had been noise-exposed to this stimulus. Here on the left-hand side of the graph, you see a single inner hair cell. I've told you that those hair cells are kind of the traditional sensory transducers in this system. They communicate their information to auditory nerve fibers through these synaptic communications. They basically release a chemical substance, a neurotransmitter that stimulates these auditory nerve fibers and transduces their signal into a form that the nerve fibers can understand.

This cartoon is showing just a couple of the nominally 20 or so auditory nerve fibers that will make single contacts with a single inner hair cell in the ear. This is a real image from a cochlea. Basically these dots here, the blue dots and the red dots just are the nuclei of these hair cells. You can see the inner hair cells in a single row here. Their nuclei are all here, they're all present. This is a very normal cochlea here. What you can see below at the bottom here of these inner hair cells are these synaptic communications. It's a little bit more difficult to see the red dots correspond to these presynaptic ribbons here. They communicate with the auditory nerve fibers through their receptors on that other membrane here.

I'm going to help you out a little bit by showing you one of those pairs of a presynaptic ribbon and a postsynaptic nerve terminal, which is in the cartoon here. Then this is a blowup of what it looks like in the real cochlea. We have these communication points at the inner hair cell. This is quite difficult to quantify at the base of these inner hair cells. There are many synaptic ribbons and lots of nerve fibers coursing in different directions. To help us out, we basically pair these ribbons and receptor patches.
Then we look at the pair of these as a proxy for a synapse. Once we have these paired communication points, we can quantify the number of these in normal ears and in impaired ears, whether it's after noise or with aging or after an ototoxic drug. You can see that this makes our quantification much easier. In each of these cells, you can see a red and a green structure here that together make a synapse. So when we quantify these, then we can see that inner hair cells, each inner hair cell has a number of these synapses at these different frequency locations.

These green dots are the numbers of synapses in an unexposed young, normal ear. Right after noise exposure, you see this dramatic loss of these communication points in a region that is most affected by the noise band here. So you see this dramatic reduction in these communication conduits. And as time goes on, we see this as a persistent reduction in these synapses in the region most affected by the noise. Whereas here at lower frequency places, there's not much effect of the noise.

So that was for one single exposure in our model. And we have since looked at a number of different exposures. We have looked at a broad range of levels and durations of noise exposure. And in these ears, basically, we quantify the threshold sensitivity. We look at those suprathreshold responses, and then we count outer hair cells and inner hair cells from the same ears. You can see that for this range of noise exposures, there is some outer hair cell loss that is concentrated in this high pitch region of the cochlea. There's not really any inner hair cell loss to speak of. The outer hair cells tend to be quite a bit more vulnerable than inner hair cells. But if we look in the same ears, we see that these synapses are dramatically reduced.

The number of synapses that are lost, at least over this range, tends to be dose responsive. So as we increased the duration of the noise, we got more synapse loss and more synapse loss. And then things started to settle down at a maximum of about 50% loss for these longer duration exposures. We can also change the dose of this noise by changing its level and keeping the duration constant. I haven't prepared a slide for that today, but obviously, noise has many parameters that can be changed.

This is just an illustration of what we see for a particular exposure, just given at multiple durations for the same noise band. So what we did then is go back and look at all of the noise exposures that we have delivered in our animal model and tried to compare them in terms of a metric that organizations like OSHA, the Occupational Safety and Health Administration, and NIOSH would use to describe noise risk in humans.

Now obviously, the measures that I'm showing you here today are being taken in a mouse and OSHA noise standards don't really have any relevance in the mouse, but it gives us a way of comparing for a given range of durations and levels of our noise exposure. And we can see what the risk is to these animals of having these noise exposures. And what we see is over a very broad range of exposures that we have looked at in the laboratory, there's really not much going on in terms of threshold elevations. In other words, there can be threshold shifts at really short post-exposure times, but over time, things start coming back to normal. And the threshold audiogram really is not showing any lasting evidence of injury until you get out to these much higher level exposures.

So in these mice then, the experimental exposures that I'm sharing with you here produced no permanent threshold shifts for a broad range of these time weighted averages. And so that basically raises the question, well, were those exposures safe at least to the mouse? And if we look at synapse counts in the same ears, the answer has to be no. So at least as far as this mouse model goes, threshold elevations are absent. They show absolutely no evidence of this dramatic underlying injury in the very same ears that's occurring for the same exposures.

I've spent a lot of time talking about noise to this point, but there are obviously other forms of acquired sensorineural hearing loss, and one of these is aging. And so this really brings me back to basically the question that motivated me to get involved in these kinds of studies to begin with. And that is, as we age, does a history of noise exposure have delayed effects on our ears? Does it change the way our ears and hearing age going forward after noise exposure? So in order to look at that, sorry, we have taken the same animal model and just studied how their hearing ages and how the structures in their ear age over the course of their lifespan.

And in this graph here, you can see that, and so these are ages for a mouse. So this is taken out to about 2 1/2 years, which is a pretty old age for a mouse. You can see that the inner hair cells, which are gray circles really stay quite close to 100% percent over this range. The outer hair cells, this more vulnerable subpopulation stays quite normal out to very late middle age and then it kind of takes a nosedive. And so outer hair cell function changes as these animals approach oldest ages. And our hearing test results that best reflect those outer hair cell injuries are shown here, and you can see that there are no shifts in that sensitivity, again, until you get into the region where the outer hair cells are becoming compromised, and then they start to rise as well. So poor threshold sensitivity with loss of outer hair cells, but intact inner hair cells in these ears.

If we look at the same ears, we can see this gradually progressive loss of those cochlear synapses here throughout the entire lifespan. And if we just take a point here, which is about in middle age, where there's no hair cell loss, no threshold elevation, we already have about 20% loss of synapses, and then it continues to decline from there. So what happens, this is what the animals look like if they've never had any intentional noise exposure, what happens now if these ears are noise-exposed first? And that was really the question that I was very interested in looking at.

So I've shown you that synapses decline gradually with age. In this high frequency region after noise, they drop immediately, they drop. So here I showed you 24 hours. We know that they drop within an hour or so after that noise exposure. This dramatic loss of almost 50% for this particular noise exposure is then maintained. And so in this high frequency region, there's almost half of the auditory nerve fibers that are not talking to anybody here, okay? They are functionally disconnected from the inner hair cells because the synapses are gone.

But if we look in this region of the cochlea that looked like it fared pretty well after that noise exposure, what we see is this delayed dropout here. So in the beginning, things look really good. It agrees with age alone. And then you start seeing declines in the synapse counts that exceed those that you would expect by aging alone. So if we look at how ears and hearing age differently after noise, we can look at different levels in the cochlea.

This beautiful image here came from the laboratory of my colleague Albert Edge, who's actually one of the scientists that works in the Hearing Restoration Project funded by Hearing Health Foundation. And you can see here, so here are inner hair cells, right? And then they are communicating with auditory nerve fibers that are leaving the inner hair cell. And then the cell bodies of those auditory nerve fibers live here in the structure that we call the spiral ganglion. I have another image of the spiral ganglion from my laboratory here in a young, normal, unexposed mouse. The cells here are much more difficult to see individually than they are in this image. They're so tightly packed. They're all there, right? And so they're all very tightly packed in this spiral ganglion.

So this is an unexposed ear. Here is an old ear that has not been noise-exposed. A 2-year-old mouse shows some dropout of these ganglion cell bodies. But if you take a mouse and noise-expose it at 16 weeks and then hold it to two years, this is what you see. And there is this really dramatic reduction in the number of cell bodies in the auditory nerve fibers that are coming to this spiral ganglion. So again, this really provides evidence that with time, a noise-induced insult has progressive consequences to structures in the cochlea. So that's all well and good.

I've talked to you about mouse models and the question is, is it a big deal in humans? Obviously, that is the question that we're now dealing with. This is a field that is fairly young. It's early days in talking about cochlear synapse loss and auditory nerve fiber loss after things like noise exposure and with aging. And so we have a number of efforts underway to try and translate these findings to humans. In this particular comparison here, we show hair cell counts as a function of age in mice and in humans. We've normalized their age to a percent of the lifespan because obviously, their actual age span is very, very different. And we've looked at different places in the cochlea. And what we see in the mouse here is really good preservation of outer and inner hair cells well into middle age, approaching older ages.

Whereas in human temporal bones, where we can go in and count the number of cells that are surviving, you can see that there is more of a loss that begins earlier and then is progressive throughout the lifespan. Similarly, if we look at the synapses or the terminals at the inner hair cells, we see the mouse, we see the gerbil again here with fairly good. I mean, they're changing with percent lifespan. They're dropping down gradually, but the human counts fall far below those of the laboratory raised animals.

So the question of course is, you know, is it something bad that these humans are doing to their ears over the course of a lifetime in comparison to the really controlled environment that laboratory raised animals live in for the course of their lifetimes. We can monitor the environment that these animals in. We of course have no way of knowing exactly what humans are exposed to over the course of their lifetime, but it is likely that they have more opportunities for exposure than these laboratory-raised animals do.

So how are we going to know, right? I've basically tried to convince you that the audiogram is not so sensitive to this hidden hearing loss. It's hidden in the audiogram. We can't really see how much synapse loss there is reflected in the audiometric thresholds. That's not to say that the audiogram isn't incredibly valuable for clinical diagnosis, it is. You saw those audiogram configurations that I scrolled through there. It describes the threshold sensitivity at the two ears by the different frequencies that we test, which are important for hearing speech, by the magnitude or the degree of the loss and by the type of loss.

You know, is it a middle ear problem? Is it a cochlear problem? And so on. And it's important to remember that all of the statistics that you hear about noise exposure, about aging, and the threshold changes that accompany these etiologies of hearing loss are in fact based only on threshold sensitivity here. So whether we consider a certain exposure to be more risky than another exposure is basically calculated on the effect on threshold sensitivity. As I have tried to describe to you, these synaptic and neural losses are not well represented in the threshold audiogram. You can have, which I showed you on that TWA graph, very large synapse losses. And as long as they are scattered and not all focused in one place, the threshold sensitivity can remain very normal, which means it will be hidden in that audiogram. It's also hidden in an audiogram that has a threshold elevation because those threshold elevations are really more related to the outer hair cell injury. They're not really reflecting the synapse loss in these ears.

So what are our options? The gold standard metric for sensorineural hearing loss quantification is the clinical audiogram, the threshold audiogram. Well, obviously there are new tools, tools that are being developed on the horizon. I've shown you these beautiful images from the animal models. On the right, you see human temporal bone tissue being stained with some of the same kinds of compounds that allow us to see structures that we are interested in.

This is the work of my collaborator at the Mass Eye and Ear, Charlie Liberman and Peizhe Wu, who are just doing remarkable work describing these changes in human temporal bones, which is really at present our only direct way of knowing what is going on underneath. So in an animal model, we can look at what the structures look like in the normal case. We can, for example, introduce maybe an ototoxic compound that kills neurons and then we can look and have histologic evidence of that. You can see the hair cells are still here but these neural

elements and the cell bodies associated with these nerve fibers are now missing in this preparation after an ototoxic insult.

Then of course, we also have physiology, we have function. And we use techniques in the laboratory and in the clinic that are highly overlapping. We test babies every day using the kinds of evoked potentials. You know, the baby is not going to raise their hand and say, I hear it, but we can put electrodes on and we can detect brain activity in response to sound in exactly the same way we can do in an animal model. We are trying very hard to develop more sensitive assays of this neural function. You can see here some key responses. I don't really have time to get into all of this today, but responses that should give us a refined look at the kinds of cells that are injured in certain kinds of etiologies of hearing loss. You can see that they can also be reported in living, breathing humans. And so that work is ongoing in the laboratory right now.

We are partnering with other labs who are looking at different kinds of responses that may be informative to the kinds of functional deficits people complain about. So for example, these auditory nerve fibers that I've talked about kind of generically at present really have very different characteristics of response. So first, I'm going to just show you how they fire spontaneously. So without any intentional sound stimulation. You will see that these fibers can be quite different. There are fibers that respond at a very low rate, medium and high rates of firing here. And these types of fibers are now being well characterized based on their composition.

People like Lisa Goodrich, who's the scientific director of the Hearing Restoration Project and one of its scientists is doing really tremendous work. So Lisa is also one of my colleagues here in Boston, and she is shedding light on the differences of these fiber subtypes that are really going to be crucial to help support the development of future therapeutics. We know that these fibers respond differently, not respond, but they fire differently in the absence of sound stimulation.

But when you stimulate these fibers with sound, they have very different response properties that have been taken as support that some of these fibers are more important in helping us hear out signals in backgrounds of noise. So things like speech in noise difficulties. For these low spontaneous rate fibers here, they can continue to code information in the presence of a background noise that for these high spontaneous rate fibers are completely saturated. And yet in quiet, it's the high spontaneous rate fibers that help us hear the very low level signals. In general terms, these high spontaneous rate fibers are important at low levels in quiet. They're basically defining the threshold audiogram. Whereas at higher levels, and especially in backgrounds of noise, it's these low spontaneous rate fibers that are helping us hear out those signals in noise.

Information like this is going to be crucial. Currently, it's very poorly characterized in the human, and so the kinds of refinements in diagnostic procedures that are ongoing in many laboratories right now will be increasingly important. So not only do we think that there is probably a vulnerable subset of neurons that is impacted by noise and by aging, but we also think that some of these, oops, sorry.

Okay, so anyway, we think that some of these losses of auditory nerve fibers are really crucial in setting the stage for some of the abnormal perceptual changes that happen and that accompany sensorineural hearing loss like tinnitus and hyperacusis. Just briefly, these are the individuals who, in many studies, have contributed to this work, not only in my laboratory, my collaborators at the Institute for Neurosciences and of course, the beautiful otopathology work that's being done on human temporal bones by Charlie Liberman and Peizhe Wu. Thanks very much.

ANIL LALWANI - Dr. Kujawa, that was an amazing talk, really. Congratulations on the body of work that is teaching us so much about the consequences of noise exposure over time. There are some questions about diagnostic tests. I know you didn't really talk about that very much, but is there opportunities? What do you think the opportunities are for diagnosing this damage? Do we need to do high-frequency testing? Where do you think the field is going?

SHARON KUJAWA - Yeah, I mean, that's the million-dollar question right now and the labs that are trying to sort that out are, so basically people have started where we did, right? You start with individuals with normal thresholds because the interpretation is easier at that point. You can have normal thresholds and then you can use a number of different techniques that can be applied pretty similarly in the animal models and in human patients.

I alluded to the fact that electrophysiology is one way that we think will help us sort this out. In other words, we can look at neural responses in the mouse and in the human in very, very similar ways. In work that I'm now collaborating with another individual at the Eaton-Peabody Lab. So Dan Polley is really an expert on behavior. Basically, on the functional consequences of different kinds of sensorineural involvements that are reflected in perception. We have been focused on what is the nerve doing? You know, what are the hair cells doing and so on.

But what does the animal hear? Is the animal hearing a signal that is more intense than you would expect for its level? So in other words, is it hypersensitive to sound after a noise insult? So we're now extending some of that work into behavior, which will get us closer to humans, right? Humans are able to give us very sophisticated judgements about the information in a signal that they hear, and they can perform tasks that give us information about how the nerves are responding to signals in backgrounds of noise, or as varied time signals.

I think it's not going to be one test. It's going to be a combination of tests that will give us information. So the tests have to be sensitive and specific, right? They have to reflect the

contributions of the different cell types that we now know are being injured. The threshold audiogram is something that is easy to acquire and it gives you great information, but it's not very good at following subtotal losses of neurons. And so we need other ways to supplement that. But in addition, we still have to have sensitive assays of those outer hair cells, because if they are injured, that means the input to the neurons is damaged as well.

So it's more difficult to sort those things out. I know it's frustrating at this point for patients but for clinicians as well. Everybody is looking for the refined combination of tests that will diagnose hidden hearing loss. I think what we're learning is that hidden hearing loss is present not only in ears that don't have any threshold elevation, it's also sitting behind an abnormal audiogram, and that's going to be the really hard situation to diagnose because you also have other kinds of injury in that ear and the diagnostic tests that we traditionally use are going to be more difficult to interpret in those cases.

ANIL LALWANI - Sharon, there's a question with the drop out of the outer hair cells, the functional drop out of the outer hair cells. Does this in any way yield insights about the development of human hyperacusis or possibly even tinnitus or any other aspects of physiology of the inner ear?

SHARON KUJAWA - Yeah, so one of the things that we are really excited about starting to look at is kind of this hyperactivity that results from these peripheral insults. So let's take noise as an example. You have an insult that we know damages the cochlea, and we know that as a result of that, the outflow, the information that leaves the cochlea is degraded, it's reduced in its amount.

There are fewer auditory nerve fibers that are carrying information. Maybe their response properties are altered. And a number of labs though have shown that that kind of reduced afferent activity, of reduced nerve activity at the level of the cochlea, instigates a gain further up in the system, where the system tries to compensate for those losses and those gain elements have been linked to abnormal perceptions.

Things like an intolerance of sounds that wouldn't necessarily be intolerably loud or the persistence of a signal that is not an external signal. So we believe that those are definitely related to, at some level, this damage in the periphery. They may get altered with time after insult, and they certainly are altered at higher levels in the auditory system, but part of this is definitely instigated in the periphery. And so we're trying to understand better what the contributions to those perceptions are.

ANIL LALWANI - So we're sort of running out of time, but I have to ask you this question. The overlap between central auditory processing disorder and hidden hearing loss and the possible role of hearing aids in this treatment. If you could provide some insight, that would be really helpful.

SHARON KUJAWA - Yeah, I mean, I think I mentioned, people have defined kind of hidden hearing loss. They've used some different terms for it in different ways over the years. And so there are definitely several forms, a number of forms of functional decline that is not well represented on the threshold audiogram. And I think that's the place where a lot of these overlap. Whether the source of this problem is central, whether it's in the brain or whether it's in the ear, it can still be not well reflected in our traditional metrics of function.

Can hearing aids help? I know that low-gain hearing aids, that's certainly not my area of expertise, but low-gain hearing aids are being trialed to try and help people have access to signals that maybe are not necessarily too soft, but they're not represented well enough in the signal they're trying to decode. For the kinds of things that we're talking about, I honestly don't know how that would help. I don't know if anybody is actually trying that yet.

ANIL LALWANI - Well, sadly, even though I think we could probably go well into the night with questions that people have asked, we have to say goodbye. Well, first, thank you for all those attended this evening. Thank you so much for your attendance. Dr. Kujawa, thank you so much for your informative research presentation on hidden hearing loss. I know that this will inspire generations of scientists that will apply for ERG funding. And so if you like to support this very important area of research, whether it's hearing loss or other things, remember that you can donate to our efforts to advance better treatments and cures for hearing and balance conditions at hhf.org/donate. And again, thank you so much everybody. And please enjoy the rest of your day.