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S1 00:00	Welcome to *Conversations in Tinnitus*, a podcast of the American Tinnitus Association. The American Tinnitus Association is a non-profit organization dedicated to research, advocacy, education, and support for people who live with tinnitus. *Conversations in Tinnitus* podcasts are an extension of ATA's magazine, Tinnitus Today, the only publication dedicated to educating the public and practitioners about ongoing research, treatments, and management of the condition. [music]
S1 00:49	Welcome to another episode of Conversations in Tinnitus. Joining us today is Dr. Jinsheng Zhang, who is a professor in the Department of Otolaryngology - Head and Neck Surgery, in the School of Medicine and jointly appointed in the Department of Communication Sciences and Disorders in the Liberal Arts College at Wayne State University. In addition to his work at Wayne State University, he also happens to be the chair of the Scientific Advisory Committee for the American Tinnitus Association. So thank you, Dr. Zhang, for joining us today for this Conversation in Tinnitus.
S2 01:23	Thank you, John. Thank you, Dean.
S1 01:26	So we're here to talk about neuromodulation today, and as we know, that can be a big topic. Neuromodulation can encompass a lot of things. The very basic understanding I have of neuromodulation from a scientific perspective is that we're essentially using some stimulus to make changes in the brain. Is that a fair statement for a very broad, sweeping description?
S2 01:50	Yes [laughter]. It is.
S1 01:53	From your perspective, what is it exactly that we're trying to do with neuromodulation when we're treating tinnitus? What is our goal for that?
S2 02:02	So if we talk about treating tinnitus, there are many ways. And commonly patients are looking for a pill, the pharmacology treatment, or pharmacological modulation. So, we will use neuromodulation-- in a layman's term, it's stimulation. Electric stimulation or other type of stimulation, a sound stimulation or magnetic stimulation. And to modulate basically the neuroactivity, if we consider that the normal neuroactivity-- the firing of neurons in different parts of the brain that contributed to the problem of tinnitus, so we want to calm down this abnormally firing activity of these neurons and so we call that neuromodulation.
S2 02:58	So, as I said, it has many forms, magnetic stimulation and we call that transcranial magnetic stimulation. And also there's another form. It's called TDCS, transcranial direct-current stimulation, and another one is we can stimulate the brain directly. We call that a direct brain stimulation. A commonly used form of direct brain stimulation is auditory cortex electro-stimulation and, so far there are a couple of ways. One is we put electrodes extradurally, in other words, these electrodes are not implanted into the brain structure, and to stimulate the areas in the auditory cortex, that's most commonly stimulated area, and the other way is intraparenchymal, so we implant electrodes into the targeted brain area to stimulate, deliver electric current to modulate those nerve cells in that area. And so it has been published by stimulation of

auditory cortex, so these are-- we consider the neuroactivity if it is not normally firing, and so we call that-- it's possible the contribution of the etiology with tinnitus or to help generate tinnitus and commonly used in the forms of-- we call that, there is a word, the maladaptive plasticity because our brain is very plastic. And following acoustic trauma that is the most common inducer of tinnitus.

S2 04:56 And so they generate, be it not wanted, not good brain plasticity. We call that maladaptive plasticity, and generally manifested in forms of hyperactivity, so the nerve cells in the brain, they fire abnormally higher than normal. So we call that hyperactivity. But also the neurons, or nerve cells, they fire-- usually they fire in a synchronized manner to perform a certain task, to generate percept or brain tasks. But if it is synchronized abnormally higher, we call that a hypersynchrony. So this is another type of abnormal pattern and also, in our brain, and (inaudible) brain, they're tonotopically organized, in other words, in the auditory system in a different part of the brain are responsible for processing the sound of the different frequencies, and [inaudible] leads to damage, and their tonotopic map, it's distorted. So, all of this is considered a maladaptive plasticity.

S2 06:13 With all these abnormally changed signals and that, we believe, based on our publications, our colleagues, and my lab, and we considered it to be the causes of tinnitus. So in order to change these abnormally firing patterns of neuroactivity into normal, so we needed to modulate. So that's why we introduced neuromodulation, and by using different forms, as I said, magnetic, electro-- direct electric current, or direct brain stimulation to down-regulate, to try to make them normal, and aiming for to bring down the percept-- or the sensation of the phantom sound, we call that tinnitus.

S1 07:07 I think there are a couple of good nuggets in there, what you just said. You mentioned that we use this term maladaptive plasticity. And of course, people talk about plasticity. There are a lot of people coming out with exercises to try to take advantage of plasticity, whether they truly work or not, but the concept, as I think you're describing it, is that the brain is reacting to something that's happened, but it's reacted in the wrong way. Because of that, we have this tinnitus created by stimulation of the auditory system that's not supposed to happen. Is that fair?

S2 07:49 That is correct. Yeah, that is correct.

S1 07:52 So, of course, we're hearing a lot about different forms of neuromodulation right now. We're certainly hearing a lot about transcranial magnetic stimulation. There's a fair amount of research coming out on that right now as well as the other methodologies that you mentioned, but essentially what we're trying to do for all these different procedures, is kind of disrupt those pathways and hope that they will then recover in normal fashion. Is that correct?

S2 08:19 That's right. Over the last, approximately a decade, there are lots of clinicians, scientists, especially clinicians and scientists they can access to a human subjects or patients to examine the therapeutic effects of these modulations. In the animal research, for example, my lab, we put electrodes in auditory cortex. We're able to down-regulate the spontaneous firing in the auditory cortex by stimulation with auditory cortex. At the same time, these animal subjects, we use a rat model, and we see the behavior evidence of a tinnitus after a noise trauma, and most common inducer of tinnitus and then as soon as the behavior evidence of tinnitus appear, we exert the electrostimulation of the auditory cortex. So we can suppress the behavior evidence of a tinnitus. So we provide the evidence from animal research, and basically, support what has been found in the clinical setting or in the human studies.

S2 09:35

And here I should have pointed out that the audience, and especially the patients, thatwhen we talk about therapies, and so that prompted me to bring up a paper published by Dr. Rich Tyler with the cluster analysis. In other words, so not every patient can benefit from one single treatment. So this treatment may work for this patient, may not work for another patient. So that's what I'm going to say. And with that said, we see lot of variability in the therapies and the studies of using the neuromodulation or all kinds of magnitude stimulations or brain stimulations. So that's why this motivation and rationale now for all the scientists

using an animal model to study the underlying mechanisms of why it works and why it doesn't work. So although we have published, and we demonstrate evidence by stimulation of a certain brain areas, but we have not come to a deeper level, for example, and in the brain there are lots of neurons and nerve cells, and there are lots of connections between different types of neurons, and so we need to do a finer job by teasing out which neurons and which they're connected neurons forming the neural pathways that are responsible for the problem with the tinnitus. And also stimulation modulating what neural pathways or what particularly neural-- in other words, we use a probing, or modulate and target particular neurons to be more specific. And to generate the optimal therapeutic effect.

S2 11:30

In fact, there is a new technology, it's called the optogenetic technique, basically we transfer a gene that expressed the option that it is sensitive to a certain light. And so we can target certain neurons to make-- to determine whether certain neurons by stimulation, that particular neural pathways can generate

optimal, or better therapeutic effect. That is under study. We have not found the definite result. It's the early stage of our study. So, this is basically along the line of neuromodulation and how it's evolving and what is the current state of science, the state of clinical results, this current situation.

S3 12:25

I'm listening to all of this very good information, this waterfall of information, this scientific data that you're continuing to collect. Have you started to get a sense of how you could tease out which method would be optimal for certain fine variabilities of tinnitus or severities, or are we still too early in stages to try and determine things like that?

S2 12:53

Yes, thank you, Dean. This question prompts me to touch on another part of this area. And right now we have actually funded a project that by testing therapeutic-- suppressing effects of tinnitus through cochlear electrostimulation-- I'm sure you audiologists are pretty familiar with cochlear implants. So basically we have animal model, we implant the cochlea of the rat. We use a rat model. And so why I bring this up, basically you can see the cochlear, and it's the peripheral, it's the ear, it's not the brain, right? But it's connected to the brain.

S1 13:40

It certainly is.

S2 13:42

It's the beginning of the auditory pathways, right? The normal ear can collect a sound and the sound signals of the ear transduced and converted to electric signals, encoded neural impulses and forwarded to the brain to generate sensation or perception, and for the presence of characteristics of a sound. And we know that basically-- so to introduce a little bit to the background of the cochlear implant, because we touch on the-- and some audience may not very familiar with this subject, because for certain patients who are hearing impaired we usually prescribe hearing aids, and through this sound amplification to help them, but for [some] patients, their hearing cannot even be helped by using hearing aids. They lose a lot of hair cells, we call that auditory nerve fibers, and that sends forward signals from the cochlea, the ear, to the brain.

And there are fewer and fewer the auditory nerve fibers left so normally prescribed auditory-- the hearing aids cannot help, so we use a cochlear implant to artificially stimulate - bypass - the malfunctional cochlea, or the ear, directly stimulating the residual [inaudible] auditory nerve fibers. And deliver the coded electric signals so that patients can hear.

S2 15:23 So because of the clinical observations from cochlear stimulation, and, by the way, it would be a restore of hearing through the cochlear implant, I'm sure. And you probably also deal with the patients who cochlear implants cannot help restore their hearing. So you bypass the cochlea by directly putting electrodes into the cochlear nucleus. That's the lower part of the auditory brain, in the brain, right, with the cochlear nucleus.

S1 16:00 Right, a brain stem implant is what they term it.

S2 16:02 Yeah, a brain stem implant, that's right. We touch on it. We published all thisfor these subjects and that helped give the audience a bigger picture of how we approach the neuromodulation. So, back to the cochlear implant, you electrically stimulate the auditory nerve fibers, and the clinicians and the patients, they together found out there are lots of patients, their tinnitus gets helped. So this brings about lots of excitement of this, the question, what's going on? So basically, recall we just been talking about the mechanism or what caused the tinnitus because of the abnormally firing neuroactivity mentioned, the hyperactivity, hypersynchrony of even increased bursting activity or distorted tonotopic map or maladaptive plasticity. So in addition to taking the brain stimulation recalled from the top and you have down, and based down the pathway projections directions, because there are lots of complex-- we cannot say signal is only top-down or bottom-up, so there's constantly up and still down and down and up.

S2 17:22 So talk about the ascending pathway stimulation of the cochlea and we also found loss for modulation, suppressing facts or therapeutic facts of tinnitus. So this is ongoing, we are finishing up collecting the data. I can update that with you and with the audience that we first implant the cochlea and we demonstrated that they have a tinnitus after noise trauma and then we demonstrated about after electrostimulation of the cochlea, their tinnitus can be down-regulated. In other words, their tinnitus can be helped and suppressed. And at the same time, we have the electrode arrays implanted in the auditory cortex. We can record those abnormally firing patterns and basically with the-- we call that neurosignals or neurosignatures of tinnitus, we found the suppression of tinnitus was accompanied by a down-regulation or decreased spontaneous firing and also the decreased synchrony in the areas in the high frequency region because we stimulated the basal turn of the cochlear, basically we stimulated the high frequency region in the cochlea, we call that tonotopic, right? So we process different frequency, low and high.

S2 18:52 And also, we published another one-- the paper a few years ago that showed by [inaudible] implant into the dorsal cochlear nucleus., and we suppressed the behavior evidence of tinnitus in rat models. And if you recall that in 1992, Soussi/Otto, they published in patients and they tried to use auditory brainstem implants to restore hearing. And they implanted it in 11 patients, I recall. And 7 out of the 11 patients, they found not only their hearing restored, but at the same time, their tinnitus-- prior to brainstem implantation, their tinnitus was measured, and after implantation stimulation, their tinnitus got helped a lot. So you can see the animal model and human studies, they can parallel. And so, plus this is the cochlear implant, dorsal cochlear implant, brainstem implant, and the auditory cortex stimulation. So all considered, it's neuromodulation, right?

S2 20:17 Back to the subject we were talking about today is to modulate and change those abnormally firing neural activity in the brain either through the top-down approach or from the bottom-up approach. If you consider, and these are proba-- consider this is invasive, it's the scientists' job and the clinicians' jobs to further improve this approach and make them less and less invasive compared to another stimulation, sound stimulation. In fact, back to the essence of the working mechanism, still modulation is the most conservative and noninvasive approach is through the sound stimulation. All taken together, we call that neuromodulation and to change the abnormally firing pattern of the neuroactivity in the brain, with the goal to suppress tinnitus to help a patient's tinnitus symptoms.

S1 21:31 Sure. And in talking about those different methods of stimulating, whether it is a top-down approach stimulating at the cortical level and having an effect, or bottom-up from the ear, how long lasting have these effects been found to be once the treatment is stopped? Is this something where people may have to undergo this for a very long period of time? Do the effects tend to be persistent and permanent? I do know that there are some people, speaking of those with cochlear implants, who have wonderful tinnitus relief when they're wearing their cochlear implant, but as soon as they can take their cochlear implant off, it comes back. So for all these different treatments, what have you seen, in the literature, is the long-lasting effect of these?

S2 22:19 Yes, remember, we talked about the variability across patients. I think I brought up Dr. Rich Tyler's paper, cluster analysis, you know, so it's up to the clinicians and scientists to do a better job to better diagnose is the problem, the etiology, what cause exactly-- what causes tinnitus of this patients, so that we can titrate a certain treatment with a target in order to have it longer lasting. So that is a still open question, and in the clinical data, some patients, when, for example, the cochlear implant, as soon as the stimulator was switched down, the tinnitus disappeared. As soon as-- certain patients, as soon as the stimulator was switched off, and the tinnitus come back, but for some patients, their tinnitus-- when you stop stimulation, and their tinnitus disappeared for a longer time, hours and even days. I don't recall-- maybe a week or so. So this is the range, and certainly it's our goal and to prolong the lasting suppression of tinnitus and how to do that. And so we need a better understanding the underlying mechanism of what causes tinnitus better. And then we develop a more targeted stimulation maybe by-- in combination of certain compounds, you know, the medicine. So basically electrical and chemical modulation and prolong the lasting suppression of tinnitus.

S1 24:12 So is that the next step for us in researching tinnitus treatments? Is it going to be combining pharmaceuticals with some of the other methods that we've discussed here?

S2 24:22 Yes, exactly, and so the animal model we-- so there are a couple papers. It's still understudied. That's why we needed to pursue it further. I'm very excited about this research and the data we're trying to publish, or what've we got, and to share the knowledge with the colleagues and general public. And so definitely, the next step, in addition, you first figure out what's the best stimulation. Electrostimulation alone, and to generate optimum therapeutic effect and we need, as you just mentioned, to find some chemical and compound and to generate a better, more potent, a more robust suppression of tinnitus. Exactly, that's important. And we just mentioned, we used the word maladaptive plasticity, and so it is generally the case in the clinical practice, and the history-- the longer the history of tinnitus, the more difficult to receive the stronger therapeutic effect. So ideally we want to conquer that and to use a more powerful modulation approach, and to change the causes of the tinnitus and to generate a more longer and more robust suppression.

S1 26:04	And even circling back around to Dean's question earlier, us as clinicians, one of our thoughts is, do you see a day when we may do a test battery, maybe including fMRI or other procedures, look at the type of tinnitus, the type of sound it is? Who knows what it will be, but have some kind of a process to then say, "Well, then this treatment looks like it would be best one for you, based on what we're finding."
S2 26:32	Yes, we call that-- that is a biomarker for diagnosis, and currently, you clinicians, we're all great at that. There is no objective, reliable objective diagnosis with tinnitus.
S1 26:50	Correct.
S2 26:51	So and our colleagues in the field are using MRI and MEG, which stands for magnetoencephalography, and EEG, and to figure out what exactly [are] the signatures of tinnitus. And there are lots of publications. There are lots because of the complexity of the tinnitus etiology, and there's no standardized or consensus that shows a certain area, the particular-- you know, light up in certain brain area roughly represent the tinnitus and what type of tinnitus and it is still-- the research and development is still develop-- is ongoing. And but so far the field have generated lots of information and basically suggesting that hyperactive, abnormally firing neuroactivity, and in the different part of the brain we talked about, the auditory systems is quite complex, quite complex already by itself. But in addition-- and there's another important area, we called it the non-auditory structures, and especially the limbic structures that are responsible for the storage of the signals, the tinnitus signals, developed and stored in the brain. For example, hippocampus, amygdala, and also response for the emotional aspect of tinnitus, and also the tension, for example the dorsolateral prefrontal cortex.
S2 28:45	All these areas are very important in the manifestations of the clinical symptoms, the clinical problems of tinnitus, and because of these areas, physiologically they are responsible for storing the tinnitus signals and developed and interacted with the auditory systems, and so in order to generate the manifestations of tinnitus. And so you consider that and so the neurosignatures of tinnitus are still being developed, and the scientists in the field are working very hard to find-- to narrow down, and so that at the treatment, our optimal treatment strategies can have been better developed. So, if you talk about the etiology, not only about the auditory system but also the non-auditory and the limbic system, limbic structures. So for the neuromodulation, back to our subject today is not only targeting the auditory system but also the non-auditory systems.
S2 30:02	So, if you talk about the non-auditory system, or limbic system, though we generally consider that's the reactive system. So, in other words this, in the brain and the presence, or the activity, within these brain structures determine how the brain reacts to the signals. If the signals of tinnitus show up, but it will be our brain, this part of the brain, and basically do not respond too strongly, then the clinical symptoms are not that severe, so maybe this helps explain those type of population, tinnitus populations, whose tinnitus are not debilitating and not bothersome. But on the contrary, if this part of the brain reacts heavily, excessively, and that's what we call that debilitating and it cannot tolerate, and the clinical intervention is then needed.
S2 31:11	Then, if you think about the working mechanism and these two parts of the brain, auditory and non-auditory, so we needed to work on both. If we work on the auditory part of the structure, and that can solve the problem of the generation of the tinnitus signals, as we can solve the generation origin of the tinnitus signals to have tinnitus in the first place. Then, if we cannot find the best modulation in the auditory system, so we can work on the non-auditory, the limbic system. So still there's lots of options if we can mitigate or diminish the reactions of the limbic structures and non-auditory

structures that respond to the presence of tinnitus signals generated in the auditory system. So we can also have a hope to generate a effective therapy for this type of patient.

S2 32:11 So you can see, by taking it together, there are lots of ways to manage tinnitus through neuromodulation. That can generate lots of hope to our tinnitus patients, and we just need time and need better research and to give a better and shorter answer. That's what the patients need, are looking for.

S1 32:36 Well, a shorter and a more specific answer. And I think that's the point. And real quick, Dean, before you ask your question, I just want to echo what you said about the diagnosis. Tinnitus is not a diagnosis. Tinnitus is a symptom. We can't diagnose it because we don't have the knowledge yet to describe exactly what is causing that tinnitus. And someday we will. We don't know when that is. And I don't say that to dishearten people who are listening. But hopefully, just the opposite, to underscore the fact that this is so very early in the process and this does take time. And it can take quite a bit of time. And we're going to stumble, but we're going to learn and we're going to keep learning and probing. And we will find these answers. And we will be able to get people this help. And someday, our grandchildren are going to look back on the things that we went through with people having tinnitus and they're going to wonder how anybody survived that because the cure, the answer is so simple, as it will seem for them at that time.

S3 33:43 Yeah, yeah. And I also want to comment, the wonderful word you used in describing those things at the very end that we're working hard, but there is hope. And when you have hope and you work hard, all of these answers, all of this clinical data that you're working on and collecting, it is going to congeal someday into very positive things where we can make a difference in people's lives, and you should be commended for that. I thank you for that. That's wonderful. I know that it's still going to take a long time, but it's very nice for John and I to hear and read all of these articles, especially they felt like they have accelerated over the past 10 to 15 years where we're collecting much more clinical data to try and get a real better picture of exactly how we can classify and treat tinnitus.

S2 34:43 Exactly, I appreciate your comments, Dean and John. It is, it is a great platform for us here and to have such interactions with clinicians, you, and me as a scientist. I just let you know that certainly why we do it in an animal model because we cannot [laughter] do lots of things in human subjects. Yeah, we can do lots of things in animal subjects, and so we can find more information, so that we can translate the know-how into the clinical trials and I can share with you, we have a number of projects going on in my lab in addition to my colleagues in the tinnitus field. Everybody's working hard. Once we go to conference, we have lots of exchanges, and basically, we're not only trying to pursue understanding of the underlying mechanism of tinnitus in order to better tease out what causes tinnitus and have a better-- develop the so-called the neurosignatures, basically, the biomarkers in the clinic. Basically, we need to find objective diagnosis. Once we have the diagnosis, basically, that's what the doctors need to do. And then you can exercise the treatment, and we have a trial right now and are developing drugs and medical devices. There are lots of exciting things going on in my lab alone. I'm sure with the ongoing efforts from my colleagues and clinician scientists and basic scientists around the world. So with ATA, this provides such a wonderful platform so that our audience can access all this information through such conversation is wonderful, and we work together to find the answer.

S1 36:49 And so we've been talking with Dr. Jinsheng Zhang, who is, again, a professor in the

Department Otolaryngology - Head and Neck Surgery, in the School of Medicine and jointly appointed in the Department of Communication Sciences and Disorders in the Liberal Arts College of Wayne State University, as well as us having the honor of having him serve as the Chair of the Scientific Advisory Committee for the American Tinnitus Association. So, thank you so much for joining us today.

S2 37:16 You're quite welcome, Dean and John.

S1 37:18 And again, I'm John Coverstone and with me, my co-host, Dean Flyger. We are honored to join you as well. Thank you for listening to this Conversation in Tinnitus and we look forward to speaking with you at the next one. [music]

S1 37:44 The American Tinnitus Association is a nonprofit organization dedicated to research, advocacy, education and support for people who live with tinnitus. Gifts and donations to ATA are used to support research for a cure and other critical missions described on our website at www.ata.org.