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Q and A with Dr. Stéphane Maison re: Vasilkov et al., Scientific Reports, 2023

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> *Editor's Note: Our Associate Editor, Dr. Steve Aiken, recently sat down with Dr. Stephane Maison about a recent study showing evidence for cochlear nerve degeneration in people with tinnitus, but normal hearing thresholds.*

A recent study from Eaton-Peabody Laboratories and Harvard Medical School found evidence for cochlear nerve degeneration in people with tinnitus and hearing thresholds in the normal range (Vasilkov et al., Sci Rep, 2023). The study included 294 people (18–72 yrs), of which 64 reported temporary or intermittent tinnitus and 29 reported chronic tinnitus. All participants had hearing thresholds in the normal range (? 20 dB HL from 250 – 16000 Hz), although those with chronic tinnitus showed poorer thresholds in the extended high-frequency range. A large set of measures were obtained, including click-evoked acoustic reflex strength and thresholds, medial olivocochlear reflexes, EcochG, and speech-in-noise measures. People with tinnitus had weaker acoustic reflexes, higher acoustic reflex thresholds, stronger olivocochlear reflexes, and weaker EcochG AP responses. This adds to the evidence that people experiencing tinnitus with normal audiograms have peripheral damage at the level of the cochlear nerve. The corresponding author, Dr. Stéphane Maison, has graciously agreed to answer our questions:

Steve Aiken: You carefully ensured that all participants had normal hearing thresholds up to 16

kHz. Yet the thresholds for those with chronic tinnitus were still significantly poorer than those in the other groups. How should audiologists use extended high-frequency thresholds to infer cochlear nerve degeneration in their clients? Is there a threshold cutoff at 16 kHz that might have reasonable sensitivity and specificity for cochlear nerve degeneration (other than the standard 20 dB HL used to define the normal range)?

Stéphane Maison: The vast majority of tinnitus patients have hearing loss, and a longstanding hypothesis of tinnitus genesis has been that hearing loss can lead to hyperactivity of the central nervous system (CNS) causing the perception of tinnitus. This hypothesis has been debated in view of the many patients reporting tinnitus with normal hearing thresholds. To clarify this apparent paradox, we designed a study to include only patients with normal hearing thresholds, as defined clinically (better or equal to 20 dB HL) and pushed further this inclusion criteria by including only those with a mean extended-high frequency (EHF) threshold ? 20 dB HL. Therefore, our sample is not designed to reflect hearing thresholds in patients with or without constant tinnitus. Rather, it is designed to 1) minimize the impact of outer hair cell (OHC) loss and/or dysfunction in the interpretation of Wave 1 amplitude and 2) to collect wave 1 amplitudes large enough to study its variability as a function of different predictor variables, including tinnitus.

Tinnitus patients following these stringent inclusion criteria were slightly older, reported more difficulties hearing in noisy environments and reported more concussion, stress and anxiety symptoms than those without tinnitus. Unsurprisingly, most of them were males. These patient characteristics are not new and can explain in themselves why tinnitus patients may present poorer EHF thresholds. It is therefore very important to consider all these variables in the interpretation of our electrophysiologic results in the pursuit of showing auditory-nerve (AN) deficits as thresholds (including at EHFs) and sex can greatly impact the amplitude of wave 1 in absence of a neural deficit. This is why we included all these variables in our regression analysis to look for neural deficits that could not be attributed to these confounders.

Let’s get back to your specific point regarding the relationship between EHF thresholds and auditory nerve deficits. Because OHCs and inner hair cells (IHCs) are mechanically coupled, any OHC deficit/loss will cause a threshold elevation and smaller AN response (this is why it is important to remove the contribution of OHC loss to the interpretation of Wave 1 amplitude to be able to infer AN loss). However, the many studies of Dr. Liberman’s lab from human temporal bones clearly show that – in normal aging patients or in those overexposed to noise, the neural loss precedes / is greater than the sensory cell loss. Therefore, if hearing thresholds are within normal limits, your patient may or may not have already a substantial loss of AN fibers that can translate into difficulties hearing in noisy environments. However, suppose you see elevated hearing thresholds in normal-aging patients or those overexposed to noise. In that case, the odds that your patient already has a great deal of AN loss is significant. This is why, in part, all patients with hearing loss report difficulties hearing in noisy environments. Animal studies have shown that the first AN fibers to degenerate are those coding for louder sounds. This is why age- or noise exposure-related AN loss will not necessarily impact hearing thresholds (unless it becomes massive) but will translate into difficulties hearing in noisy environments.

Here, we show that patients with constant tinnitus and normal hearing thresholds have a significant loss of AN fibers (as inferred by a decrement in wave 1 amplitude) after accounting for the loss of sensory cells, sex and concussion. This result clarifies the paradox we evoked earlier, i.e., all tinnitus patients have a peripheral deficit (seen or not on the audiogram) and is consistent with the idea that tinnitus arises as a result of a maladaptive plasticity of the CNS (brain hyperactivity)

triggered by a loss within the peripheral auditory system.

Aiken: What I like about your work is your thoughtful changes to traditional diagnostic measures. The method you used to measure the acoustic reflex (from your earlier work with Mepani et al., 2020) is based on reflected energy from a click stimulus and a wideband elicitor—instead of the standard approach of a 226 Hz tone with pure tone elicitors. Using this method, you've found evidence for a relationship between reflex thresholds and word recognition, and now between reflex thresholds and tinnitus. What are the best options for audiologists who may want to use acoustic reflexes to assess nerve degeneration in the clinic? Is work planned or underway to incorporate this new method in clinical devices?

Maison: There are a number of companies offering wideband tympanometry (WBT) these days as a method to diagnose middle-ear disorders (e.g., titan from Interacoustics). We chose WBT because the standard approach to perform tympanometry and assess the middle-ear muscle reflex (MEMR) is highly variable and offer poor sensitivity. This would not be my method of choice to assess nerve degeneration as, despite the increased sensitivity of this method (you can get a MEMR threshold as low as 45 dB SPL!), the variability remains way too large to infer cochlear nerve degeneration on an individual basis, not to mention that hearing loss greatly impacts your ability to measure the reflex.

Aiken: Another interesting approach is the separation of the EcochG into high and low frequency portions to disentangle the AP from the SP. You've proposed that an early part of the neural response overlaps with the SP, and that this is why the SP (thought to primarily reflect cochlear potentials) appears to be associated with cochlear nerve degeneration in some human studies. If this is correct, we may want to use this filtering approach whenever obtaining an AP/SP ratio in diagnosis. Have you had a chance to consider how small the AP/SP ratio should be for an audiologist to suspect cochlear nerve degeneration?

Maison: There seems to be a little bit of confusion here. The idea is to get the cleanest possible way to assess AN loss.

Historically, there's been many ways to assess Wave 1 amplitude. First, by assessing the baseline – AP peak amplitude. This method is not good enough as it includes the SP. We know now that the SP arises from 4 generators of different polarities: the sensory cells (OHC – IHC), the non-spiking and spiking neural potentials (e.g., Excitatory Post-Synaptic Potentials, Action Potentials) (DOI: 10.1152/jn.00006.2019). So, any measure including the SP comprises hair cell receptor potentials. Second, by measuring the AN response from the inflection point between SP and AP to the AP peak. The latter is tricky (particularly when there are multiple inflection points) and attempts to develop objective measures of the latter failed (DOI: 10.1121/10.0006572). It also removes from the measure the neural components of the SP. 3) Measuring N_1P_1 includes the early responses from the cochlear nucleus and therefore is not "purely" auditory nerve.

To address these issues and obtain objective measures of the AN responses under computer control (as opposed to visual inspection of the waveform), we recently proposed a filtering method that consists in measuring band-passed filtered ABR waveforms (see, DOI: 10.1121/10.0017328). Why?

Using a Fast Fourier Transform, we can obtain a spectral representation of ABR waveforms. The latter has 3 peaks, including one near 800 Hz. This 800 Hz peak is absent in patients that carry

Otoferlin mutations. These patients have no synaptic vesicle release from the IHC and cannot produce APs. The electrical noise recorded at the round window in quiet shows a peak at 800 Hz that disappears when spikes from the AN are pharmacologically blocked. The single-neuron contribution to a gross potential derived by cross-correlating the spontaneous spike trains of single AN fibers with the round-window electrical noise has a periodicity of 1.25 msec which produces a spectral peak near 800Hz. For all these reasons, we believe that this 800 Hz peak reflects the neural spiking activity of the auditory nerve. So, in our most recent studies, we chose to separate the neural spiking component of ABR responses from other generators by filtering our waveforms with a bandpass filter.

Steve Aiken: You didn't find an increased wave V/wave I ratio in the chronic tinnitus group as might be expected if tinnitus was associated with increased central gain. On the other hand, you did find this gain increase in the low-pass filtered response (3–470 Hz). How do you interpret that?

Maison: Indeed, this is something we discussed in the paper. We believe it's a downside of using our filtering method. If you look at Wave 5 prior to using our bandpass filter, it is much wider. Therefore, Wave 5 includes energy at low frequencies that are likely to be filtered out by our bandpass (470 Hz – 3000 Hz). To capture this low-frequency energy, we looked that the low-pass filtered response of ABRs (3 Hz - 470 Hz) and indeed observed that tinnitus patients had larger responses at Wave 5 latency, consistent with increased central gain.

Steve Aiken: In your conclusion, you suggest that diagnostic assays of cochlear nerve degeneration might be useful for planning tinnitus treatment in the future, and also for tracking treatment efficacy. Do you see any current clinical value in assessing cochlear nerve degeneration for people with tinnitus?

Maison: In cochlear synaptopathy / CND, the synapse between IHCs and the AN is affected but the soma and central axons can remain alive for decades. In mice, applying neurotrophins to the round window can rescue AN function and reduce synaptopathy after noise-induced hearing loss. Any attempt to investigate the efficacy of such approach in humans will require audiologic tools to assess nerve function before and after treatment. In tinnitus patients, the idea is that neural regeneration using neurotrophin-based therapies may reverse the central hyperactivity resulting from nerve loss and perhaps reduce the tinnitus percept in combination with central approaches (retraining).