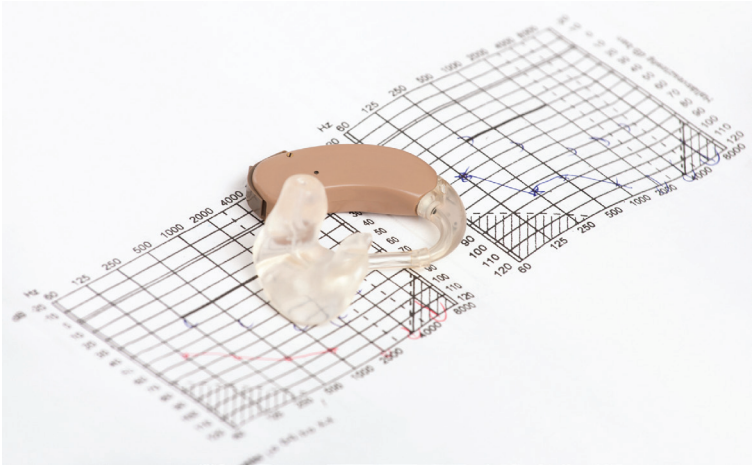
Not-So-Hidden Hearing Loss

By Nina Kraus, PhD, & Travis White-Schwoch

SG Kujawa and MC Liberman published a paper that instantly became a modern classic (**Kujawa. *J Neurosci* 2009;29[45]:14077-14085**). They exposed mice to a single, moderate-level noise for two hours—enough to cause a temporary threshold shift. Indeed, they documented this shift through distortion product otoacoustic emissions (DPOAEs), auditory brainstem responses (ABRs), and compound action potentials (CAPs).

Shortly thereafter, DPOAEs thresholds returned to normal, but the ABRs and CAPs remained affected. Careful histological analyses of the noise-exposed cochleae showed the hair cells were left intact, but even after thresholds returned to normal there was an acute loss of afferent nerve terminals. The ear was healthy, but the connections from the ear to the brain were lost forever.



andras_csontos/iStock

Subsequent work has shown a similar effect following a life of moderate noise exposure (**Sergeyenko. *J Neurosci* 2013;33[34]:13686-13694**), and that this neural degeneration targets the high threshold, low spontaneous rate nerve fibers that fire in noise (**Furman. *J Neurophysiol* 2013;110[3]:577-586**). Thus, an animal can have a normal audiogram and normal hair cell function despite a profound loss of the neural infrastructure thought to be critical for auditory processing in noise (although this remains to be shown empirically).

This so-called or "hidden hearing loss" (or "cochlear neuropathy") has captivated auditory scientists, and provides an elegant hypothesis for the cause of age-related hearing difficulties (**Ruggles. *Curr Biol* 2012;22[15]:1417-1422**; **Plack. *Trends Hear* 2014;18**), auditory processing disorder (**Bharadwaj. *J Neurosci* 2015;35[5]:2161-2172**), tinnitus (**Schaette. *J Neurosci* 2011;31[38]:13452-13457**), and hyperacusis (**Hickox. *J Neurophysiol* 2014;111[3]:552-564**). Additionally, understanding this pathophysiology can point to a clinical strategy for pharmacological interventions if ever a drug be discovered to regenerate synapses. Several researchers have argued that hidden hearing loss is a widespread phenomenon in humans and are working to discover a diagnosis, and have argued that this work has important clinical implications—including in *The Hearing Journal* (**Zeng. *Hear J* 2015;68[1]:6**).

While this work points to a compelling hypothesis about everyday communication, we believe several fundamental questions remain, many of which pose a bottleneck to clinical translation (**Zeng. *Hear J* 2015;68[1]:6**):

- It has been posited hidden hearing loss explains age-related hearing difficulty, auditory processing disorder, tinnitus, and hyperacusis. How does a single injury manifest (at a minimum) as four distinct pathologies? What are the factors that lead two people to suffer the same acute injury, but develop different phenotypes? How does this peripheral injury interact with predispositions, lifestyle factors, and cognitive factors such as attention or working memory in contributing to patient outcomes?
- An analogy has been drawn between hidden hearing loss and auditory neuropathy, the latter of which is characterized by normal hair cell function with an absent ABR. Many authors have suggested that hidden hearing loss is akin to a mild form or auditory neuropathy, especially given the presumed behavioral consequences of the peripheral deafferentation. This analogy fails to consider a competing hypothesis for neuropathy, however, which suggests these listeners have plenty of afferent synapses that simply fire dyssynchronously (**Starr. *Brain* 2003;126[Pt 7]:1604-1619**). The dyssynchrony hypothesis is supported by computational modeling of neuropathy. Additionally, the protein otoferlin has been implicated in neuropathy because it regulates synaptic vesicle release at the afferent connections to inner hair cells (**Roux. *Cell* 2006;127[2]:277-289**), but is not necessary for ribbon synapse formation. Finally, we note an extremely rare but fascinating syndrome, temperature-dependent auditory neuropathy. These listeners exhibit transient auditory neuropathy when they have a fever, but their auditory function is otherwise essentially normal (**Starr. *Ear Hear* 1998;19[3]:169-179**). We highly doubt they undergo an immediate deafferentation when febrile and reafferentation when their temperature returns to normal. Together, this evidence questions the extent to which hidden hearing loss is similar to auditory neuropathy.

Dr. Kraus, left, is a professor of auditory neuroscience at Northwestern University, investigating the neurobiology underlying speech and music perception and learning-associated brain plasticity. **Mr. White-Schwoch**, right, is a data analyst in the Auditory Neuroscience Laboratory (**brainvolts.northwestern.edu**), where he focuses on translational questions in speech, language, and hearing.

Dyssynchronous synaptic activity at the inner hair cell afferents would be qualitatively distinct from a loss of those afferents.

- What are the consequences of a peripheral deafferentation for central auditory function? Caspary and colleagues have documented a profound loss of inhibitory neurotransmission in older animals that they have long since hypothesized may be a maladaptive compensatory gain for the loss of afferent input (**Caspary. *J Exp Biol* 2008;211[Pt 11]:1781-1791**). This hypothesis is supported by recent work by Polley and colleagues, who attribute many of the communicative difficulties experienced by listeners with auditory neuropathy to maladaptive central plasticity as opposed to peripheral deafferentation per se (**Chambers. *Neuron* 2016;89[4]:867-879**). These observations are also consistent with work in humans that shows, for example, that older adults with normal hearing thresholds exhibit poor neurophysiological processing of sound (**Anderson. *J Neurosci* 2012;32[41]:14156-14164**).
- How would a diagnosis of hidden hearing loss guide treatment in the clinic? There are no ways to regenerate neurons, and although there are efforts to develop a drug much more research is required. If somebody has normal thresholds, they are likely not a candidate for amplification and certainly not for implantation. Listeners already know that they have problems hearing in everyday settings—what they are looking for is a strategy to improve their listening success.
- This leads us to our last question. Just how hidden is hidden hearing loss? We define it as a hearing problem that cannot be explained by a threshold shift on the audiogram, but we all know the audiogram is not a good measure of everyday listening skills. There's nothing hidden about a patient who struggles to understand speech in everyday environments—in fact, that's pretty blatant. Perhaps we would be better off thinking of this as "not-so-hidden hearing loss."

What are the factors that lead two people to suffer the same acute injury, but develop different phenotypes?

This work provides game-changing understanding into potential mechanisms underlying listening difficulties, and has posited elegant hypotheses that make strong predictions about factors contributing to these difficulties. But while this work may one day offer strategies for diagnosis and management, many questions stand between not-so-hidden hearing loss and the clinic.