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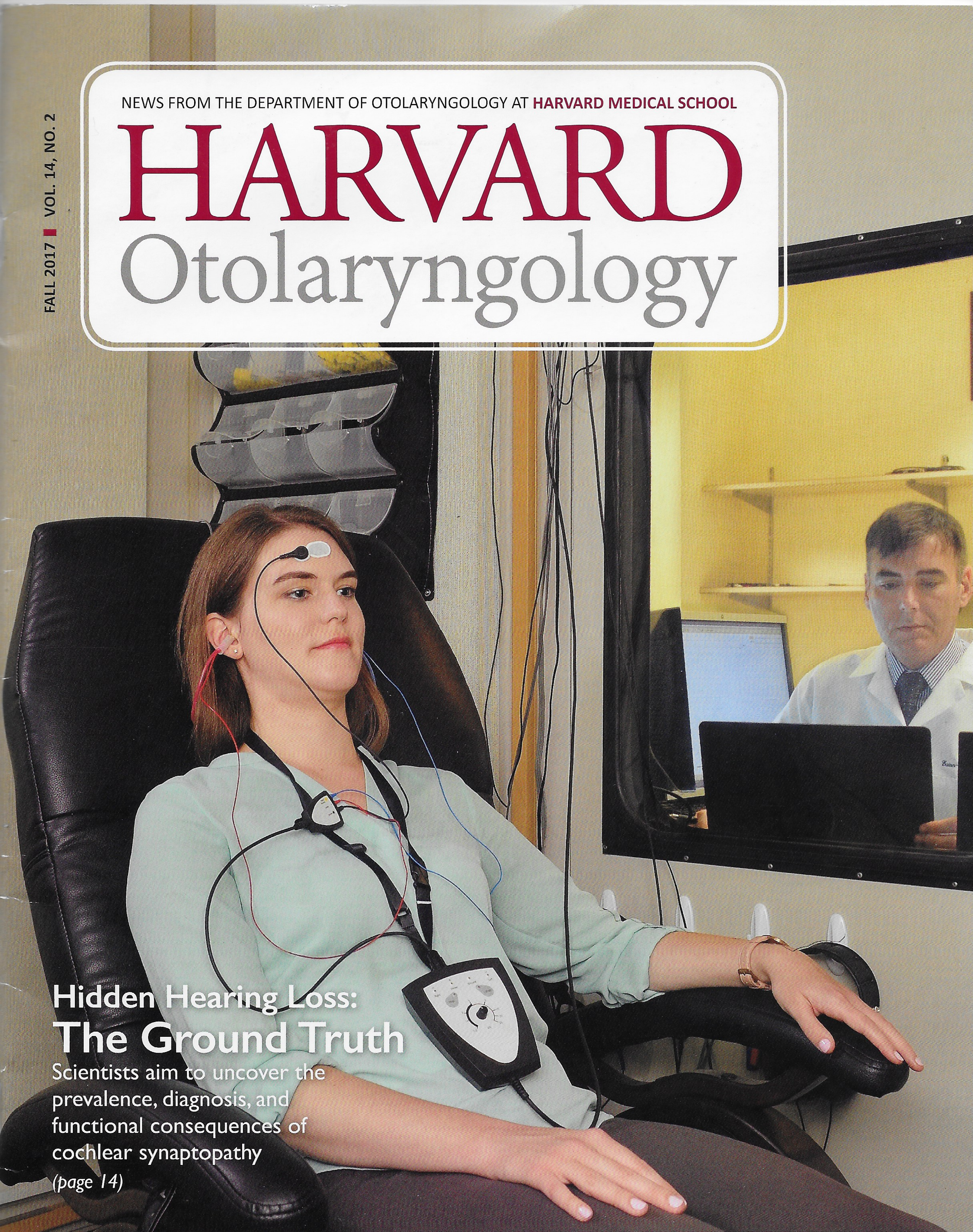

Hidden Hearing Loss: The Ground Truth

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Hidden Hearing Loss: The Ground Truth

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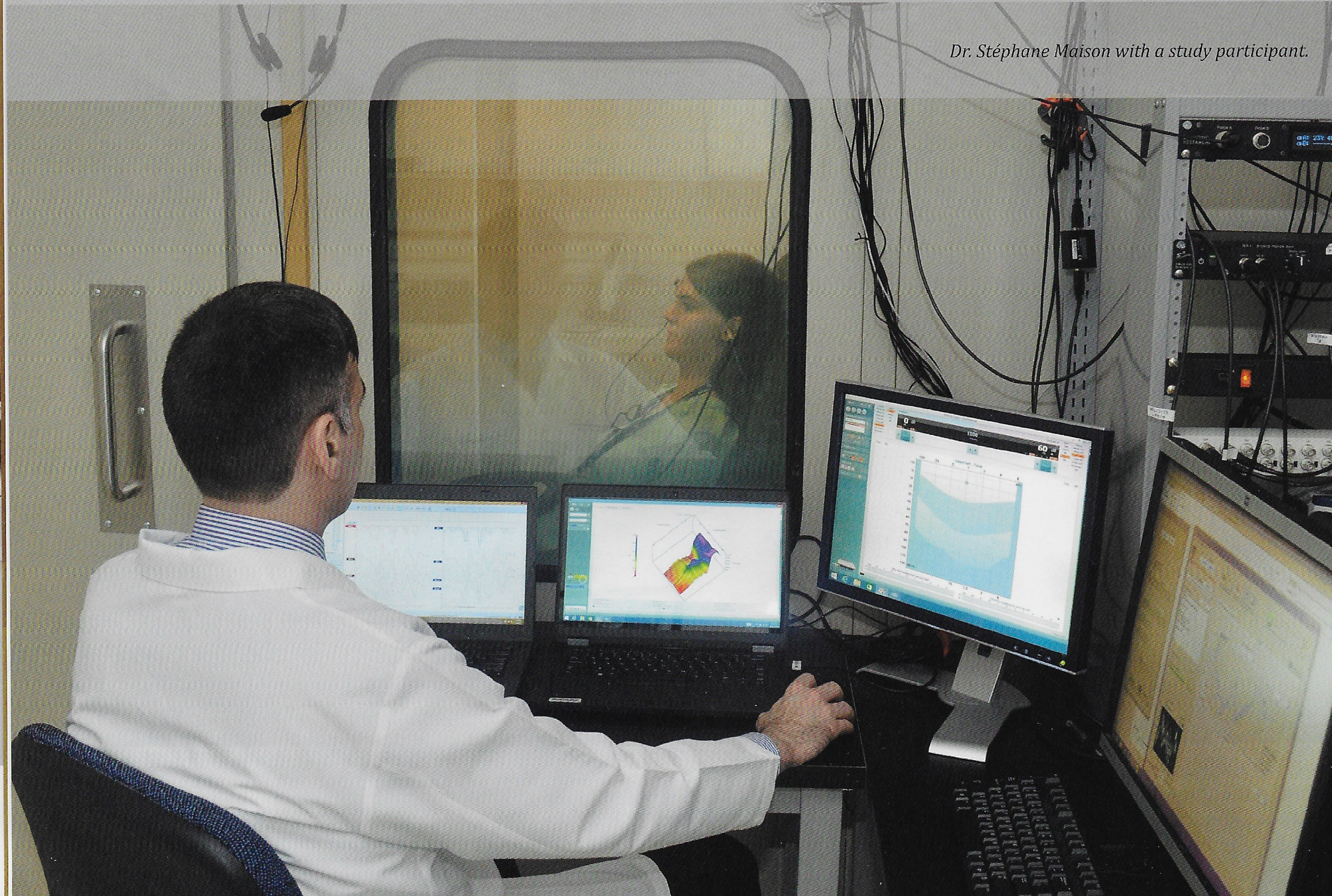
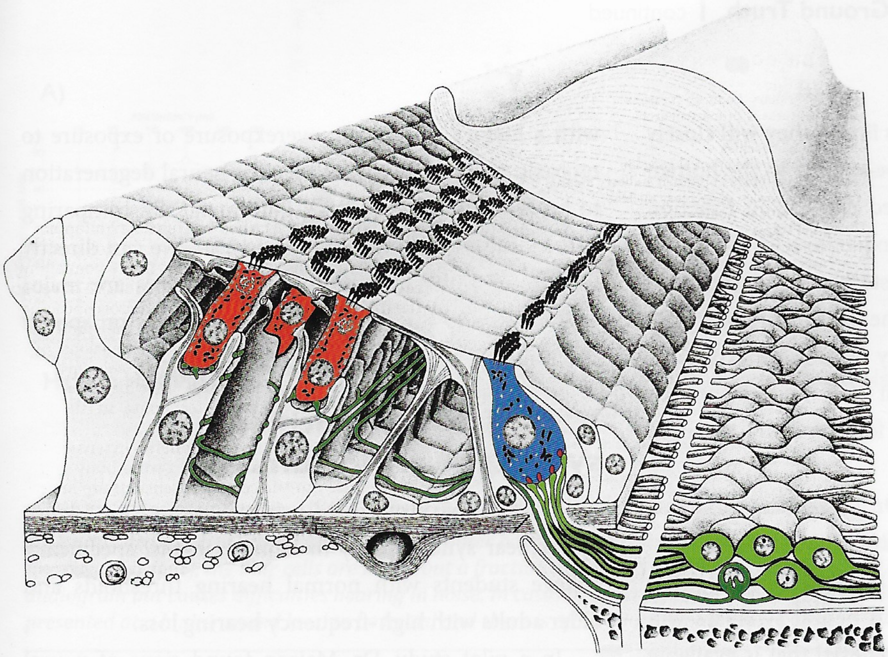
For years, clinicians and auditory neuroscientists have assumed that hair cells are the most vulnerable elements in the inner ear. Hair cell damage is typically the cause of hearing loss, as detected by the threshold audiogram (the gold standard test of hearing sensitivity); however, it's been noted that two individuals with the same audiogram results can have very different hearing handicaps—notably, the ability to understand words in a noisy environment.

It wasn't until a research team led by Sharon G. Kujawa, PhD, and M. Charles Liberman, PhD, of Massachusetts Eye and Ear/Harvard Medical School, uncovered a new type of inner ear damage that this phenomenon could be easily explained. In 2009, they found that the neural synapses responsible for communication from the ear to the brain are actually the most vulnerable structures in the inner ear. With age or noise exposure, many of these synaptic connections can disappear and decrease the fidelity of the auditory information sent to the brain.



Dr. Stéphane Maison with a study participant.



Artist's rendition of the normal structure of the inner (blue) and outer (red) hair cells in the inner ear that turn sound vibrations into electric signals in the fibers of the cochlear nerve (green).

Kiang NYS. Peripheral neural processing of auditory information. Compr Physiol 2011, Supplement 3: Handbook of Physiology, The Nervous System, Sensory Processes: 639–674. First published in print 1984. doi: 10.1002/cphy.cp010315.

"Previously, we thought that neural loss happened only after hair cell loss," said Dr. Kujawa. "What we learned, however, is that damage to neural synapses can occur without permanently affecting hair cells or audiometric thresholds. This makes it undetectable by a standard audiogram, which is one reason it was undiscovered for so long."

Known as cochlear synaptopathy, or hidden hearing loss, the degree and extent of this nerve damage in human populations has yet to be determined. It's been linked to difficulties understanding speech in noise and is thought to instigate tinnitus and hyperacusis. But in order to properly treat it, clinicians must also understand its prevalence and functional consequences.

With support from a National Institutes of Health (NIH) P50 grant, Dr. Kujawa and Dr. Liberman, along with Stéphane F. Maison, PhD, AuD, CCC-A, and Daniel B. Polley, PhD, also of Mass. Eye and Ear/Harvard Medical School, are combining their efforts to explore these mechanisms. Through four projects, the investigators will work toward the refinement of diagnostic measures in human populations, which will be essential in assessing future therapies to repair the nerve damage.

"With the help from this grant, we are aiming to uncover the full extent of this disorder," said Dr. Maison. "There's evidence supporting the idea that cochlear synaptopathy may have major implications in understanding many inner ear diseases, so it's possible that our work will influence the way many patients are treated in clinic."

Translating insights from animals to humans

Since this nerve damage cannot be directly assessed in living humans, the first two projects will measure the degree of cochlear nerve damage in animal models and human ears obtained at autopsy. Both projects will study cases of the most common causes of acquired sensorineural hearing loss (SNHL) in humans, which include 'normal' aging, noise exposure, and ototoxic drugs.

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>
> **—Dr. Kujawa**

In previous work, the investigators have provided clear evidence of early and progressive synaptic and neural loss with age and after noise exposures that only temporarily changed hearing thresholds and had no hair cell loss. With project one, Dr. Kujawa will examine consequences of noise and ototoxic drug exposures in animal models over varying degrees of damage—from temporary to permanent, and with and without hair cell loss and threshold sensitivity loss.

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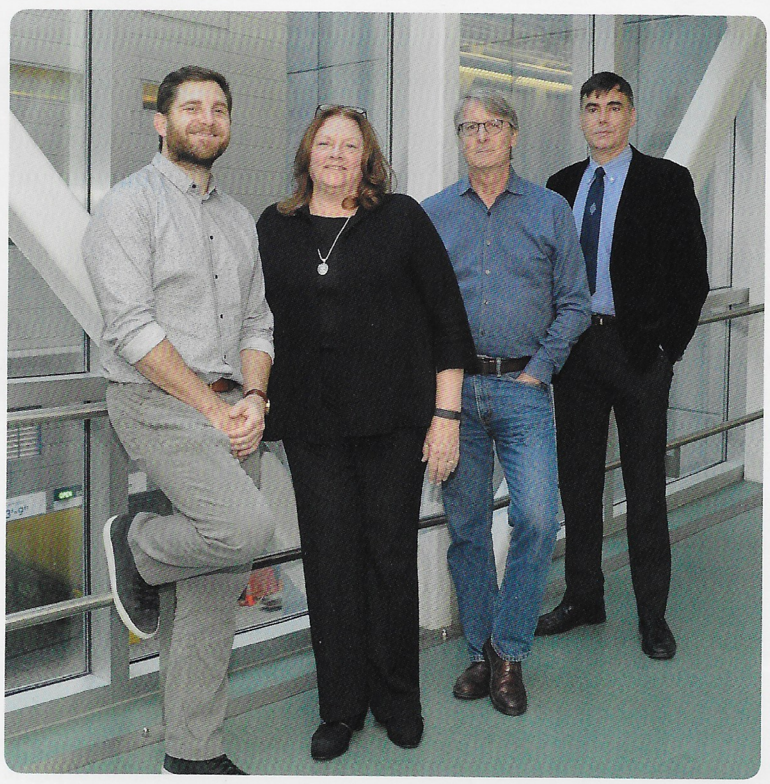
A key feature of these studies is that they will closely mirror the techniques that will be applied in the human studies to assess exposure-related changes in function and characterizing the underlying injury. In doing so, the diagnostic power of the tests can be determined directly by comparison with the histopathology. The researchers expect that the injury from these exposures will be widespread and that it will be reflected as abnormal function, particularly for responses acquired in background noise.

The second project, led by Dr. Liberman, will focus on quantifying the loss of neurons and hair cells in human subjects. With the use of modern immunostaining approaches, the hair cells and neural synapses will be counted in archival autopsy material that is available through the Temporal Bone Bank at Mass. Eye and Ear, which is the largest collection of human inner ear specimens in the world. The degeneration patterns will be compared to audiograms and speech-in-noise scores obtained in the same subjects prior to death.

"Our working hypothesis is that, in 'normal' ears, we will see dramatic degeneration of the neural elements with increasing age before the loss of hair cells. In cases with a history of acoustic overexposure or exposure to ototoxic drugs, we expect to see the neural degeneration to be even greater," said Dr. Liberman. "By comparing these results with the audiometric tests, we can directly test the idea that differences in neural loss are major contributors to the performance decrements on speech recognition tests."

Drs. Daniel Polley, Sharon Kujawa, Charles Liberman, and Stéphane Maison.



Understanding cochlear synaptopathy in humans

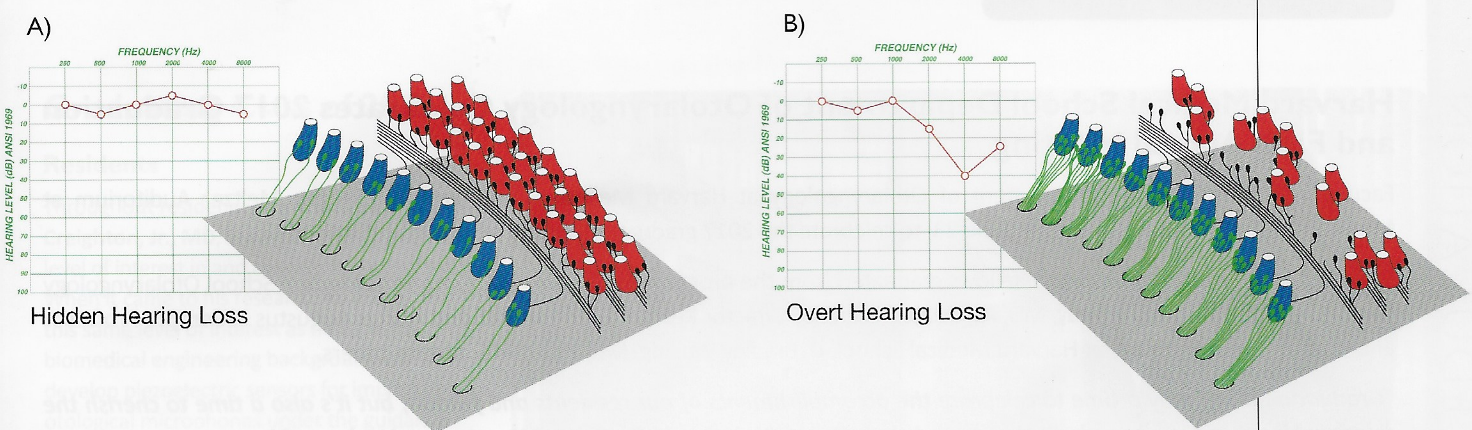
The final two projects will involve looking for evidence of cochlear synaptopathy in living humans, specifically college students with normal hearing thresholds and older adults with high-frequency hearing loss.

In a pilot study, Dr. Maison found signs of neural damage in young adults with repeated exposure to loud music that were correlated with increased difficulties understanding speech in noisy environments. Dr. Maison is extending this study in project three to administer, in a large cohort of adults with normal audiograms, a test battery aimed at finding the best test combination that can predict signs of cochlear synaptopathy in a clinical setting.

The same test battery will be repeated over a five-year period in a cohort of young musicians with regular and continued acoustic overexposure to track how signs of cochlear synaptopathy and difficulties understanding speech in challenging environments progress over time.

"Our previous work suggested that young people with a normal audiogram and continued ear abuse already experience signs of neural damage and increased difficulties hearing in noisy environments," said Dr. Maison. "We are now offered the opportunity to implement, in a large-scale population, a series of tests that will help define diagnostic criteria to identify candidates for neuroregenerative therapies that may be on the horizon."

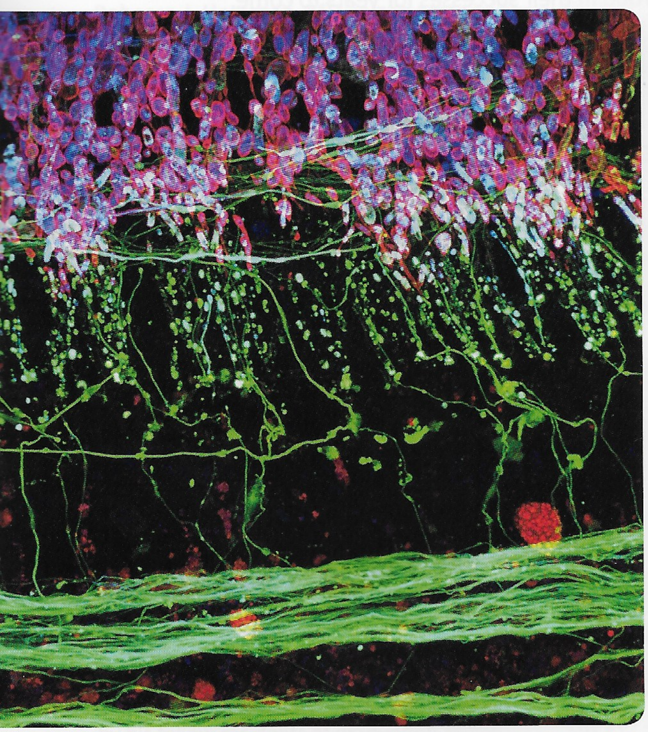
The final project, led by Dr. Polley, will aim to explain the longstanding conundrum that two people with identical down-sloping audiograms can have different hearing abilities, as seen with responses to word recognition



Schematic drawings of inner hair cells (blue), outer hair cells (red), and cochlear nerve fibers (green) showing that in Hidden Hearing Loss (left), the hair cells are intact but a fraction of the nerve fibers have disappeared. This causes no change in the threshold audiogram but causes difficulties hearing in noise. In cases of Overt Hearing Loss (right), the audiogram shows that tones must be presented at a higher sound level to be heard and there is often a loss of hair cells.

tasks. It is thought that this variance might be caused by hidden differences in the neural processing of low-frequency signals that convey speech information.

"We want to identify the neural signatures of tinnitus and impaired speech recognition in noise," said Dr. Polley. "This could help us detect the underlying pathology in patients with explicit hearing loss and better understand the brain's response to a loss of input from the ear."



Cochlear nerve fibers can be seen in the inner ear of a normal-hearing human, removed at autopsy. This image was obtained using a confocal microscope after treating the tissue with antibodies to a type of protein present in all nerve fibers (green) and with a dye that marks the myelin sheaths surrounding them (red).

Since the most common complaints from patients suspected to have cochlear synaptopathy involves speech and noise, both projects three and four will measure how individual subjects understand speech by tracking speech outcomes and neural predictors over time. Whereas project three will track the decline of neural processing and speech recognition in individuals exposed to high levels of noise, project four will track improvement through the use of an interactive audiomotor training interface that was programmed by Dr. Polley.

Moving toward a diagnosis and treatment

In addition to uncovering more about cochlear synaptopathy, preliminary work has also suggested there may be an opportunity to rescue the lost connections and reconnect nerves and sensory cells. Therefore, the investigators are also thinking about treatment strategies.

In order to start treating patients, proper diagnostics will be needed first. Only with a reliable diagnosis will clinicians be able to choose the right candidates for clinical trials and determine the efficacy of a treatment. The researchers are optimistic that their work will bring us closer to both goals.

"We believe that cochlear synaptopathy is present—and a problem—in many individuals," said Dr. Kujawa. "We're hopeful that our work will provide important insights that will lead to better diagnostics and treatments for our patients."

Current Biology

Audiomotor Perceptual Training Enhances Speech Intelligibility in Background Noise

Highlights

- Elderly subjects trained for 8 weeks on a computerized audiomotor interface
- Speech-in-noise intelligibility in challenging listening conditions improved by 25%
- Generalized training benefits were compared to and exceeded placebo effects
- Inhibitory control ability and game strategy predicted individual training benefits

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In Brief

Whitton et al. put the "real-world" usefulness of computerized perceptual training to the test in a randomized, double-blind, placebo-controlled study. They report that hearing-impaired older adults can triple the speech intelligibility benefits of their hearing aids in challenging listening environments after training on a custom audiomotor game.