Observations from the 2017 Association for Research in Otolaryngology Midwinter Meeting
Dr. Iver Juster

The Association for Research in Otolaryngology (ARO) held its annual "mid-winter" meeting in Baltimore. The ARO's mission is "…encouragement and promotion of research, both basic and clinical, in the broad field of Otolaryngology and related areas; to foster friendly assembly and stimulate scientific interest among its members." The Mid-winter meeting convenes researchers, students, educators, clinicians and patients; and covers a wide spectrum of topics mostly related (but, as the name implies not limited) to hearing and balance.

Hyperacusis Research organized a dinner meeting, the Next Steps for Hyperacusis event, to convene people with personal, clinical or research interest in hyperacusis. Bryan Pollard's excellent and comprehensive write-up of this meeting is posted here: http://hyperacusisresearch.org/2017-aro-hyperacusis-next-steps. The meeting focused on:

- Growing mutual understanding and collaboration amongst key stakeholders (patients and those in their lives; clinicians; academics and researchers)—with the goals of increasing public awareness and informing the research agenda
- Updates on current state of hyperacusis-related research using the Roadmap to a Cure framework
- Launching the Hyperacusis Alliance, which has since met three times (see Bryan's article for the Alliance's rationale and goals)

This article is a personal report of and perspective on hyperacusis-related topics from the conference and the dinner meeting. I'm a medical generalist with interest and experience in medical informatics[1] and health economics[2], and I'm motivated—and inspired--by people in my life who struggle with hyperacusis. Like all perspectives, mine inherently includes certain omissions, biases and possible inaccuracies (I'm not an otolaryngologist or hearing science researcher). I invite readers to point out any they may find.

Organization of this report

- Highlights
- Experiences of people with hyperacusis
- Research on peripheral mechanisms
- Research on central mechanisms
- Intriguing research on the first synapse (connection) between the peripheral and central auditory system, which may hold a key to early detection. Pathology or dysfunction of a synapse is called a *synaptopathy* (sin-ap-TOP-a-thee, where the 'th' is pronounced as in 'think')

Throughout: Making connections and "**I wonder**…" questions

Highlights

- Participation at the Next Steps for Hyperacusis event offered an exemplary model for all-stakeholders collaboration, combining the voices of patients, people in their lives, academics, clinicians and researchers
- The ARO meeting itself is research-focused and offered a window into the methods used to explore normal and disordered hearing in humans and animals. Many methods used to peer into this window are feasible only in animal models. I've developed a deep appreciation for the ingenuity with which animal researchers model hyperacusis and tinnitus (and profoundly grateful to lab animals[3] and human subjects)
- *Hyperacusis* is a term that refers to elevated sound sensitivity and does not indicate a "disease" (specific pathologic process) any more than fever or headache. Hyperacusis may variably present with pain, tinnitus, hearing loss, and other symptoms. Research may need to take these variations into account.
- There's increasing evidence that hyperacusis-related pain is mediated by the small, unmyelinated Type II afferent neurons that synapse on the cochlear OHCs. Unlike the larger and far more-numerous Type I afferents (that synapse on the IHCs), these neurons don't carry auditory information. Why some people develop pain is unknown but I believe we're seeing hints that genes related to cell receptors for neurotransmitters could play a role.[4]
- It's worthwhile to think of the auditory system—and of places where pathology may develop and treatment may be targeted—in 3 parts: (1) the peripheral auditory system (cochlea including hair cells); (2) the central auditory system (including the neurological pathways and processing waystations of the spinal cord, brainstem and brain); and (3) the central-peripheral meeting place—the Types I and II synapses of the acoustic branch of the eighth cranial nerve on the hair cells.
- There are profound interactions among these domains, which may both explain why hyperacusis develops in some but not others; whether it includes pain or tinnitus; how it is maintained (being seemingly resistant to resolving); and opportunities for treatment
- Some progress is being made in understanding what may be needed to improve or restore the function of the peripheral components. This may potentially include fabricated, bioengineered or regenerated hair cells; or manipulation of the cochlear environment (e.g. of local inflammation)
- Surgical reinforcement of the cochlear oval and round windows is gaining popularity as a way to reduce the impact of hyperacusis. It's early days but several patients have reported positive results (and some haven't). Researchers are investigating what types of patients are best-suited and how durable the results.
- Screening (early detection of an existing condition before it's clinically apparent) of people at high risk for hyperacusis could become a reality based on research on 'hidden' hearing loss and studies showing that people don't notice hearing-related symptoms until most of their cochlear nerve fibers are lost. If practical screening tests can be developed, we may be able to prevent hyperacusis from developing.
- There's considerable research activity around central mechanisms specific to hyperacusis and more generally, around pain. Through efferent pathways, activity in the

higher-up (closer to brain) CNS can influence activity in the lower CNS and periphery. Experiences of hyperacusis and pain are intertwined with activities in the parts of the brain that serve attention, memory, emotions and internal clocks. *Central sensitization* may be a big part of hyperacusis (as it is known to be in chronic pain), where the "gain" is "turned up" as the CNS attempts to compensate for what it sees as reduced auditory input from a damaged periphery.

Definitions and abbreviations used in this report
CNS: Central nervous system (brain, brainstem and collections of neuron cell bodies ('nuclei') and their neurons; and spinal cord
Afferent pathways carry information from the periphery towards CNS and brain
Efferent pathways carry information from the brain or CNS towards the periphery
IHC: Inner hair cells of the cochlea (On which Type I afferents synapse)
OHC: Outer hair cells of the cochlea (On which Type II afferents synapse)
CN: Cochlear nucleus
AC: Auditory cortex (of the brain)

Why are we doing this? Experiences of people with hyperacusis

Through a hyperacusis Facebook forum, people with hyperacusis were invited to attend the dinner meeting, or to share thoughts in advance. A person with hyperacusis offered moving insights into "what it's like" – see Bryan Pollard's article for her account; we're fortunate as clinicians and researchers to have such articulate and committed patients—it's essential for the funding and success of our work. Family members of patients as well contributed their experiences and concerns. The use of plastic plates and utensils contributed to a hyperacusis-friendly and aware environment.

Pre-conference questions from the hyperacusis Facebook group:

1. What are emerging areas of research. Which do you see as most promising and why?
2. Is hyperacusis research overlapping with, converging or sharing ideas with other types of research such as basic neuroscience, tinnitus, hearing loss and neuropathic pain? (See notes from 2016's ARO hyperacusis symposium which focused on pain)
3. Do most researchers think hyperacusis stems from one type of mechanism (such as mechanical disruption of sensors) or is it more an in-common result of many mechanisms?
4. Is there evidence that pain-including hyperacusis has a fundamentally different mechanism than the type that does not include pain?
5. Is there a difference in the likelihood or pace of recovery for those with pain-hyperacusis?
6. Sound sensitivity is measured with pure tone discomfort levels. Yet many people with hyperacusis say that they are greatly bothered by sounds at much lower intensities than their pure tone tests would predict. Can we test that kind of sound sensitivity?

- Inform and prioritize the research agenda
- Develop and use assessment and outcome measures that reflect the dimensions of the hyperacusis experience that may not be accurately captured on current tests (examples: types of pain; symptom variability; discomfort thresholds for non-pure tones[5]). What's "most important to measure" varies depending on the purpose of the metrics—for example, screening and prevention,[6] diagnosis, prognosis, monitoring the effect of treatments (or the natural history) or correlation with basic research
- Arm patients with an accurate and useful understanding of what research is and does, the ways it goes about finding questions and attempting to answer them, the basic kinds of studies and their strengths and limitations, and how to interpret a research report

While I have the pulpit: More questions about pain hyperacusis

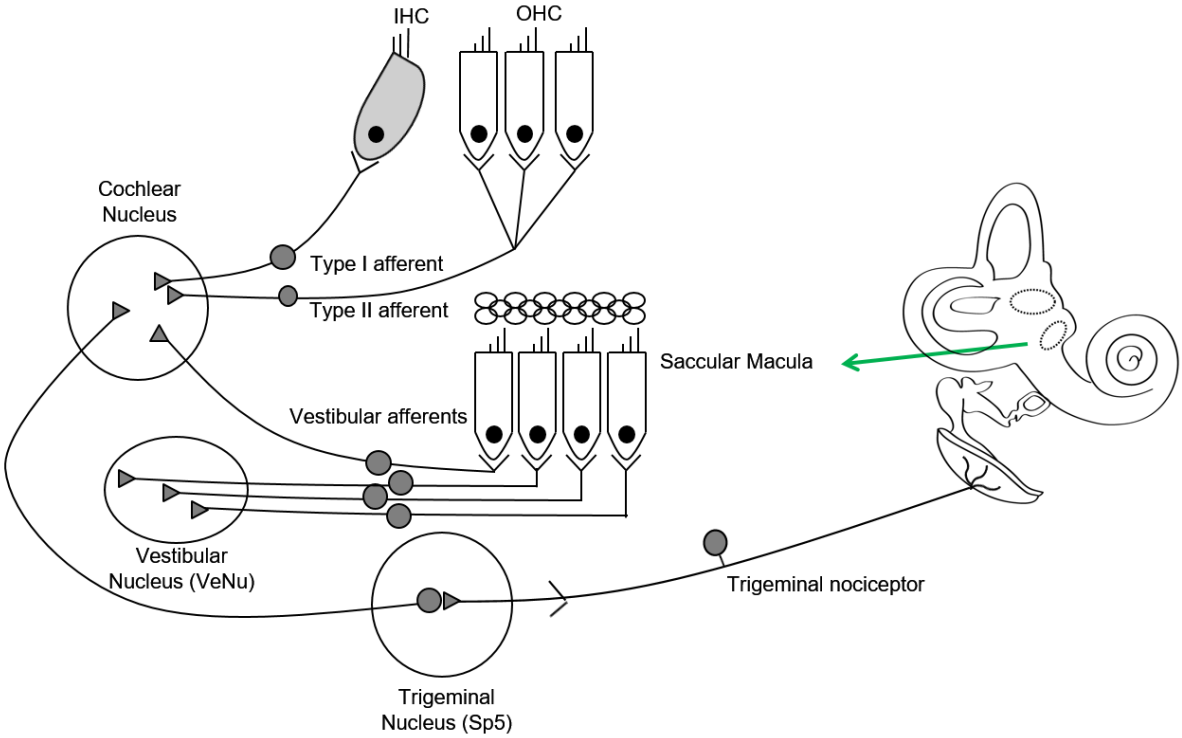
7. Anatomically and physiologically, is the experience of pain in hyperacusis served by the periphery (middle and inner ear or sensory afferents enroute to the first waystation, the cochlear nucleus); or the central waystations and processing centers ascending to the brain; or in the brain itself? Or…?
8. Does the answer to the above vary over the time-course of hyperacusis (for example, more peripheral early on, then becoming more central as the condition becomes established)?
9. Does the location and physiology of pain vary with the cause of hyperacusis (e.g. single vs. multiple loud sounds, chronic sound exposure, infection, toxin exposure)?
10. At what point(s) does the initial "insult" develop a self-reinforcing stability (such as irreversible peripheral injury or central sensitization)?
11. Are there neurologic workarounds, such as alternative neural pathways that could bypass damaged or dysfunctional ones, in which such patients would be amenable to training the workaround-pathways and thus partially or wholly alleviating hyperacusis? This occurs in other conditions like heart failure, heart attack or stroke
12. How does a person's genetics or exposures (at a point in time or over time) of hyperacusis be viewed as a pattern or complex fingerprint and what are the implications for treatment?

Sensing the auditory environment: Research on peripheral mechanisms

At the Next Steps meeting, Jaime Garcia-Aňoveros focused on the peripheral component – *auditory nociception* – and the "detection of cochlear damage (such as that produced by intense or persistent noise) by the Type II afferents." He focused on the genes that regulate proteins used by Type II afferents; brain areas other than the cochlear nucleus that contribute to auditory nociception, and how, specifically, nociception mediates pain.

To provide a framework for doing research on determinants of pain in hyperacusis (which likely vary among individuals), he diagrammed our current understanding of the auditory pathways and methods researchers do or could use to provide a window into what is occurring at each place on this pathway. Here's Jamie's picture of the peripheral auditory pathways through their connections to the first central waystations (the cochlear, vestibular and trigeminal nuclei)—anatomical locations where hyperacusis might arise or could be affected. He stepped us

through these various locations and pathways, showing how animal researchers could systematically observe the effects on "noxacusis" (auditory nociception) of specifically knocking out the function of each component. It was found that knocking out IHC, Type I afferents, vestibular afferents or the trigeminal nerve didn't affect behaviors associated with noxacusis—this left the Type II afferents as the peripheral mediators of pain hyperacusis.



Jaime's schematic shows the biological pathways that could potentially be involved in auditory nociception ("noxacusis"). The cochlea's inner hair cells (IHC) carry nerve impulses along Type I afferents to the first central waystation—the cochlear nucleus; Type II afferents carry nerve impulses from the cochlea's outer hair cells (OHC). Type I are far more common than Type II (20:1 ratio) and larger, well-insulated nerves suitable for rapidly transmitting high volumes of detailed information—they carry sound (acoustic) information afferently (towards) the brain. Until recently the role of Type II afferents has not been understood, but their structure does not support rapid transfer of detailed sensory information. Rather—like similarly-structured nerve fibers elsewhere in the body—they are structured to carry information about noxious (dangerous) stimuli. Researchers have developed ways to isolate (functionally delete) various parts of the system that could potentially underlie noxacusis. The idea is that if a part of the system is blocked and the animal continues to display noxacusis behavior, the conclusion is that that part doesn't play a role in noxacusis. If on the other hand blocking a part stops the noxacusis behavior, it is reasonable to infer that that part does play an essential role in noxacusis—and to the extent that animal and human auditory systems behave similarly, we gain insight into how pain hyperacusis works for humans, at least at the peripheral level.

In addition or in combination, protective reflexes could incite noise-induced pain; and neurogenic inflammation could cause pain or reduce the intensity of noise energy required to induce pain.

I wonder: It's important to recognize that while researchers have found that Type II afferents and the cochlear OHC are integrally involved in noxacusis, the *actual* experience of pain hyperacusis is more complex. We need to understand why people's thresholds for initiating

hyperacusis vary so much; to what extent the noxacusis mechanism remains involved in pain hyperacusis over time; whether repairing the dysfunctional peripheral mechanism for noxacusis would reduce pain hyperacusis (does pain hyperacusis set up a self-sustaining central mechanism that could not be reversed by fixing the periphery, assuming that was possible?); and the extent to which the answers to these questions varies with different people, different causes of hyperacusis, and time.

I also wonder: Given what seems to be the same stimulus, why do some people acquire hyperacusis and some don't? If we could understand and identify the variations in susceptibility, perhaps we could warn high-risk people to take precautions, as we already do for people with risk factors for other conditions. Or as noted in the section below on synaptopathies, we may soon have effective methods to screen for neurological antecedents of hyperacusis. Examples of risk-factor candidates may include: genetics, past noise exposure, history of tinnitus, past or current exposure to environmental toxins (such as heavy metals or pesticides), dysfunctional metabolism (to some extent measurable by markers in blood or urine). Does pain hyperacusis involve the peripheral nervous system (hair cells, Types I and II afferents) in a fundamentally different way than non-pain hyperacusis? What does this imply about the role of the periphery, or of the various levels in the central nervous system (i.e., from the cochlear nucleus on up to the brain), or of 'descending' or efferent pathways from the various levels of the central nervous system that modulate the activity of the ascending pathways)?

Could bioengineered or even 3-D printed cochleae (or OHC) restore or improve hyperacusis?
As a thought experiment, suppose the only permanently dysfunctional tissue was damaged hair cells or their synapses on Type I and II neurons (see section below on synaptopathies). Now, suppose we could make a theoretically-perfect hair cell replacement able to re-form functional Type I and II neural connections. Then (in this thought experiment) we should be able to cure hyperacusis, because any central component would be functional (not permanent)—that is, it would have developed solely as an accommodation to (or consequence of) what had been permanently damaged—the cochlea.

This *thought experiment* motivates research on hair cell functional restoration, regeneration or replacement:

- *Functional restoration:* Partially or fully restoring the biological capabilities of hair cells (including their synapses on Type I or II neurons) so that they stop doing (or do less of) whatever dysfunctional hair cells do to create hyperacusis (especially pain hyperacusis). Examples (at least potentially): altering fluid dynamics in the scala tympani in patients with superior canal dehiscence, a rare condition that results in hyperacusis[7]; reducing inflammation in the cochlea; improving the metabolic environment in and around the cochlea (this may involve nutrition and reducing toxins—at least in theory); stimulating repair or regeneration with low-level laser light
- *Regeneration:* Transforming a damaged hair cell to a functional one. Potential examples: Injecting growth factors into the fluid bathing the hair cells (thus creating an environment favorable to them becoming anatomically and biologically 'normal'); use of stem cells (which could work by producing growth factors or by differentiating into

normal hair cells); genetic engineering (introduce genetic material that gives hair cells instructions on how to become healthy)

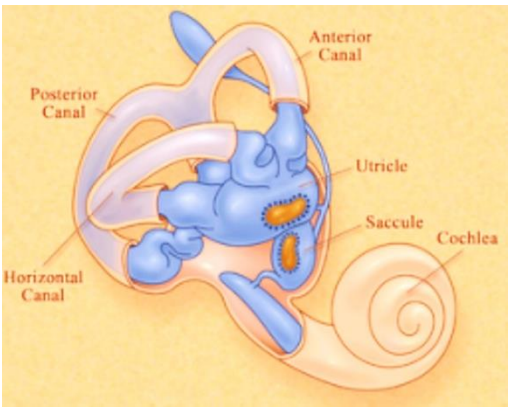
- *Replacement:* Introducing cultured (biological) healthy hair cells or engineered functional replacements. Examples: Nano-engineered or 3-D printed functional or biological tissue. While 3-D printed heart, kidney and liver tissue is starting to be explored, it might be possible to engineer a device that performs the requisite function, as cochlear implants do for hearing. To improve hyperacusis, such replacement tissue would have to function in a way that prevents whatever damaged or dysfunctional cochlear structure do that results in the biological train events giving rise to hyperacusis.

These strategies may sound various degrees of futuristic, but I wouldn't be surprised to hear that some of them are farther along than we might think, or that technologies other than these are (or will be!) in development and improve the lives of people with hyperacusis, as suggested by several speakers in a symposium on studying the inner ear via ingenious 'models' in vitro (outside the body).

For example, **Don Dongeun Huh**[8] presented on "Microengineered physiological biomimicry: Human organs on chips," leveraging microfabrication and microfluidics to develop simplified tiny non-biological models of tissues or organs that enable researchers to study how organs respond to changes in the environment. He demonstrated this idea in microengineered models of the lung, surface of the eye, placenta and cervix. For more, see the NIH's National Center for Advancing Translational Sciences (https://ncats.nih.gov/tissuechip/projects) and a TED talk at https://www.ted.com/talks/geraldine_hamilton_body_parts_on_a_chip.

Potentially complementing non-biological microengineered models are hybrid in vitro (outside the body models that combine biologic and non-biologic materials. **Else Vedula, Danielle Lenz, Abigail Spencer, Brett Isenberg, Tj Mulhem, Albert Edge, Erin Pararas and Jeffrey Borenstein**[9] presented on an in vitro 'platform' that supported hair cell viability, attachment and replication. The platform allowed them to study the effect of surface shape, toxins and fluid flow on electrical potential in inner ear progenitor cells (more-primitive cells that give rise to hair cells). They referred to their hybrid platform/cell environment as a 'biomimetic cochlea.'

Another in vitro study focused on how inner ear cells communicate by signaling among themselves. **Lisa Cunningham, Lindsey May, Elyssa Monzack, Andrew Breglio and Shimon Francis**[10] looked at the cell-cell interactions of hair cells with inner ear supporting cells and traveling cells called macrophages. These interactions may occur by direct cell contact or through chemical messenger molecules. To do this work, they used mouse utricles (part of the inner ear that serves balance). The work is relevant because these biological interactions determine whether hair cells live or die when exposed to various stresses. To illustrate, heat shock protein (HSP) is induced by the stresses of heat, acid-base balance (pH), starvation, free radicals and mechanical damage. Generally, HSPs are protective—they inhibit cellular death as well as toxicity from certain antibiotics. I wonder if people who developed hyperacusis were genetically less able to express HSPs under stress?



http://www.webalice.it/maio_nunziata/vertigine.htm. The utricle responds in a way that is a good predictor of how other tissues in the body (including the inner ear) respond, and has the advantage of being able to harvest as a whole organ

Attention is rising both in otology and biology overall in the role of the *extracellular matrix* (ECM)—the collection of substances secreted by cells to provide structural and biochemical support to the surrounding cells.[11] **Peter Santi, Alec Brown, Sebahattin Cureoglu and Helge Rask-Anderson**[12] reported that the while ECM probably plays a role in normal hearing, we know little about how it interacts with cochlear cells. A better understanding might be relevant because in other tissues, the ECM has been shown to be directly involved in cell proliferation, differentiation and polarization of epithelial cells. In addition, genetic and environmental factors can modify the composition (and therefore the function) of the ECM.[13]

While we're waiting for researchers to come up with a foolproof way to repair, replace or regenerate damaged or dysfunctional hair cells and their immediate connections the auditory nerve, we do know that anyone can use ear plugs to render sound (somewhat) more tolerable by partially blocking its effect on the tympanic membrane – the vibration of which transmits sound information and energy through the middle ear's three bones and round window (RW) to the fluid-filled cochlea. However, ear plugs have practical and possibly biological drawbacks. Recently, neurotologists have introduced a procedure in which the round and oval windows of the cochlea are reinforced with various types of tissue to render them stiffer (presumably more resistant to sound energy); many but not all patients report their sound tolerance improving.

This procedure has been used to treat superior (labyrinth) canal dehiscence for many years; it was found that the hyperacusis often associated with SCD lessened afterwards. It's early days for this procedure in non-SCD hyperacusis; though early results look promising **I wonder** how durable the results will be; which types of hyperacusis are best suited to the procedure; and whether some types of hyperacusis may be worsened.

Xiying Guan (mentioned above) and colleagues Song Chen, Deepa Galaiya, John Rosowski and Hideko Nakajima[14] presented on the effect of RW reinforcement on hearing (Xiying also presented the model at the Next Steps event). The researchers wondered why some people who get RW reinforcement surgery experience worsened hyperacusis; and what happens to their hearing.

Using fresh human cadaver cochleae, they developed a model and a metric—the "cochlear input drive" (ΔP) —that compared the pressure in 2 contiguous (but not connected) inner ear fluid spaces – the scala vestibuli (Psv) and scala tympani (Pst). They then defined the metric as ΔP = Psv-Pst (that is, cochlear input drive = the pressure difference between that in the scala vestibuli compared to the scala tympani). They conceptualized ΔP as an estimate of hearing (as explained in the diagram). To assess the effect of RW reinforcement, they used the stapes velocity (Vstap) (as it vibrated in response to various sound frequencies and intensities).

After RW reinforcement, they found a decrease in Vstap at frequencies below 1 kHz, suggesting that RW reinforcement increases its impedance (resistance to movement). By itself, this ought to dampen sound-energy. However, because of relative changes in the 2 compartments' pressures, they concluded that the procedure either doesn't change—or might increase—hearing at low frequencies "and thus can worsen how-frequency hyperacusis." They noted little effect on their modeled measure of hearing at higher frequencies.

I wonder: If I interpret their conclusions correctly, they translate the effect on (their model of) hearing to the potential effect on hyperacusis, but do we know from measured correlations of hearing and LDLs at various frequencies in patients who've had the procedure? It seems that more patients report benefit than report no benefit (let alone actually worsening)

I also wonder: In this experiment, only the RW was reinforced; however, the procedure in practice usually reinforces both windows. Does this make a difference? And, how is reinforcing the windows fundamentally different in effect from using high-quality ear plugs (ones that reduce sound energy in a way that preserves fine distinctions rather than simply muffling it)?

Central mechanisms in development and maintenance of hyperacusis

Paul Fuchs[15] further illuminated the question of *efferent* neural pathways:

- One group (medial efferents) synapse on OHCs and if activated, inhibit cochlear activity
- A second group (lateral efferents) synapse on Type I afferents (the fast-conducting neurons that carry sound information upwards from IHCs); their function is unknown
- In addition, he pointed out research that found that Type II afferents are poorly stimulated by the chemical messenger used by Type I (glutamate) but rather they respond strongly to hair cell damage
- **I wonder:** Taken together, the current evidence about the peripheral (Type I and II) afferents and efferent pathways point to a major role for the outer hair cells, Type II afferents, and efferents in underlying the experience of hyperacusis pain. Is "What are

the differences in these pathways for people with hyperacusis who do versus who don't experience pain?" a priority topic for research?

Work on peripheral mechanisms contributing to hyperacusis (and especially pain hyperacusis) must proceed apace with investigation of central mechanisms; and as is true for development of chronic pain in other contexts, pain of peripheral origin ultimately engages the central nervous system as well. This phenomenon is often referred to as 'central sensitization' or 'development of increased central gain.' It's well-known that central involvement in the experience of pain can involve centers in the brainstem, the ancient deep brain (including those that play roles in attention and emotion), and the cerebral cortex (associated with our conscious perception of sound and pain).

For example, **Senthilvelan Manohar**[16] discussed animal models for identifying and distinguishing pain hyperacusis from avoidance hyperacusis (presumably the latter represents hyperacusis without pain). Clearly this work contributes to our need for developing a deeper understanding of the peripheral and central mechanisms underlying pain hyperacusis – especially when we're confident these models really do parallel human experience.

I wonder whether the effectiveness (usually reported in the 6-9 dB LDL range) of cognitive-behavioral therapy in some people with hyperacusis reflects the contribution of central pathways; and if so, whether people with pain and no pain respond equally well. I further wonder what part of central mechanisms CBT (when it works) modifies. I hope there is more than a few dB to be gained from getting at central sensitization and gain!

Dorit Mohrle, Kun Ni, Dan Bing, Ksenya Varakina, Ulrike Zimmermann, Marlies Knipper and Lukas Ruttiger[17] presented on how noise- or age-related hearing loss may be involved in the development of tinnitus or hyperacusis by inducing changes in CNS activity patterns. They already had mouse models for tinnitus and hyperacusis based on the animals' behavior, and induced hearing loss through noise exposure or age. They then measured changes in hearing threshold, auditory processing of sounds louder than the hearing threshold, and OHC function. In addition, they applied special techniques to observe the hair cells for any changes. They concluded that "the development of tinnitus and/or hyperacusis involves a distinct failure to adopt the central responsiveness and an insufficient compensation of the reduced cochlear output after auditory overstimulation." In other words, people who develop tinnitus and/or hyperacusis after noise exposure or as they age experience a dysfunctional level of central adaptation.

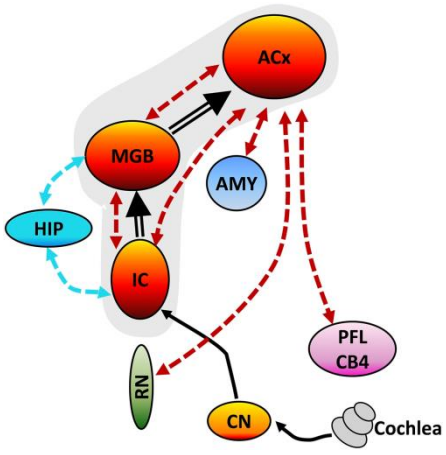
In fact, another study[18] of age-related hearing loss (in mice) was presented that found that the inferior colliculus (a processing waystation for afferent sound information) showed increased sound-evoked activity, rendering it hyperexcitable. **I wonder** what differentiates those who do vs. those who don't develop this dysfunctional central adaptation (or perhaps develop it more easily than others)?

The neurobiology of hyperacusis and the concept of central sensitization or inappropriate "central gain" was further illuminated in a presentation by **Guang-Di Chen, Kelly Radziwon, Benjamin Auerbach and Richard Salvi**[19] that found that gain—greater energetic output for a

given unit of input—was higher in the auditory cortex and lateral amygdala in noise-exposed rats (this study also identified different changes in neural activity in animals that developed recruitment rather than hyperacusis, and suggested that both findings indicate that the auditory cortex and amygdala play a role in loudness perception). Highly relevant to the experience of people with hyperacusis, the amygdala is the "integrative center for emotions, emotional behavior and motivation."[20]

How can we gain useful (accurate, testable, and potentially impactable) insight into the locations and pathways underlying central processes in hyperacusis—in humans, where detailed anatomical, physiological and electrical measurements that can be used with laboratory animals are not practical (or dangerous)? Requisite to that is precise localization in the human central nervous system. **Rebecca Dewey, Susan Francis, Deborah Hall and Christopher Plack**[21] presented on precision localization of subcortical structures in the central auditory pathways using MRI-related technology—something that has been difficult to do. Their purpose was to use imaging technology to measure the effect of short-duration noise exposure and "low-level" chronic noise on hidden hearing loss. If these effects can be measured reliably, we could better understand the extent to which typical environmental noise exposure can lead to tinnitus and hyperacusis.

I wonder if the new generation of much-quieter MRIs could be used for imaging research on people with hyperacusis (or anyone who doesn't want to acquire it!). For example, 3-Tesla machines (the magnet strength used in this research) can produce well over 100 dB intermittently for up to 45 minutes, but both GE and Siemens (and to a lesser extent, Toshiba)[22] are installing machines that produce sounds in the 70-80 dB range. Combined with ear protection (and when appropriate, mild sedation), could these machines bring patients with hyperacusis to the research table? **I wonder:** For reasons unclear to me, it can be challenging to find imaging centers that use these "much quieter" MRIs—you'd think they'd market this advantage (I've read that the second commonest complaint about MRIs—after the tight space—is the noise).



Richard Salvi[23] discussed strategies for understanding neural networks related to hyperacusis, using four tools—positron emission tomography, magnetic resonance imaging, magnetoencephalography, and quantitative electroencephalography. The image shows the auditory CNS locations and pathways for which these tools may provide insight.

I wonder how good we will get (and how we'll get there) at aligning structure (anatomy), neurobiology (e.g. the chemical messages known as neurotransmitters, and metabolic pathways), function (what happens in hyperacusis) and the person's experience?

Richard illustrated aligning anatomy and function with a functional MRI study in which giving sodium salicylate (similar to aspirin) induced tinnitus and hyperacusis and increased functional connectivity. Richard cited a 2017 mapping study that showed tinnitus distress is linked to enhanced functional connectivity between the limbic system (role in emotions and emotional memory) and the auditory cortex.

ACx: Auditory cortex; AMY: Amygdala; MGB: Medial geniculate body; HIP: Hippocampus; IC: Inferior colliculus; PFL: Prefrontal lobe (of the cerebral cortex); CN: Cochlear nucleus.

Take-away: Imaging strategies can reveal changes in connectivity among places (and therefore roles) in the central nervous system—at least when hyperacusis is induced chemically.

When peripheral auditory components—the cochlear hair cells and their afferent nerves—are damaged, the 'de-afferentiated' central auditory neurons can become hyperexcitable. Left unchecked, this response would simply increase central gain (more output for same level of input), causing sounds to be perceived as too loud and distorted. **Jennifer Resnick and Daniel Polley**[24] looked at how the cerebral cortex 'compensates' for damage to the auditory nerve by both inhibiting too-strong and strengthening too-weak auditory inputs from the lower central auditory system following damage to the cochlea. This neuroplastic response represents the brain's way of striving to return to a normal balance (homeostasis). Using lab mice and various levels of sound injury, the researchers found (a) an initial disruption of the brain's ability to modulate the distorted auditory input coming from the damaged cochlea, followed by (b) partial-to-full return of cortical homeostasis—longer for a more intense sound injury. Importantly they found that the degree of return to homeostasis in the first few days predicted how fully cortical sound processing returned months later. The authors said "These findings underscore the central importance of inhibitory dynamics in the recovery of function after sensory nerve damage…. However, of all the markers of cortical plasticity, inhibitory tone was the only measure that never fully recovered to baseline following moderate or profound cochlear denervation. Thus, recover of sound sensitivity might introduce unstable circuit dynamics associated with tinnitus or hyperacusis."

I wonder if early intervention at the brain-processing level in newly-acquired hyperacusis might help ameliorate the long-term consequences. If so, research should be directed towards illuminating what that type of intervention could be, and focusing on identifying hyperacusis within days of its occurrence (unfortunately, not the typical scenario).

A study by **Aaron Apawu, Avril Holt et al**,[25] found that dopamine (a neurotransmitter or chemical messenger) may have something to do with promoting central gain; and hints that the cellular receptors for dopamine may be influenced by noise exposure. **I wonder if** genetic variability in receptor function and noise-tolerance may be at play.

On the topic of neurotransmitters and their cellular receptors, **Katrin Reimann, Dorit Mohrle, Marlies Knipper, Lukas Ruttiger, et al**[26] studied the cyclic GMP (cGMP) signaling pathway in the inner ear—which has been reported to facilitate protective processes in response to trauma. They found this pathway to be protective after noise exposure. **Opinion:** Our understanding of both the forest (pathway interrelationships) and trees (detailed neurobiology, physiology,

anatomy and genetics) of 'inner ear' disorders is accelerating and (with adequate funding, prioritization and collaboration) I'm optimistic for a bright future.

Can chronic exposure to noise levels typically found in our daily lives cause hearing loss, tinnitus and hyperacusis? If so, what mechanisms might be in play? A study by **Adam Sheppard, Guang-Di Chen, Dalian Ding and Richard Salvi**[27] didn't address that question directly but importantly found that our typical sound environments could result in turning up the CNS gain. Previous work showed that lab mice continuously exposed to 75 dB broadband noise for five weeks experienced neurologic changes typical of central gain. Now the researchers found similar changes at 65 dB—midway between normal conversation and the sound from a shower or air conditioner[28] (a toilet flush is said to be 75 dB, though from personal experience I'd gauge some in commercial locations to exceed 80-85 dB…and don't get me started on hand-dryers).

The researchers did not find hair cell changes, so **I wonder** if central gain effects resulting in tinnitus or hyperacusis could occur with sustained sound levels that don't cause hair cell damage, or may perhaps make it easier to acquire hearing disorders with less hair cell damage. In today's world, sustained exposure to sound levels above 70 dB (frequently punctuated by much louder sound) is very common. For example, it is said that a passenger car traveling at 65 mph generates 77 dB 25 feet away; mid-morning freeway noise at 50 feet generates 76 dB, and a vacuum cleaner generates 70 dB. I typically record: 85 dB in a jet airplane at cruising altitude (a little ahead of the wing); 70-85 dB in a busy airport; and 80-100 dB inside a subway (kudos to the upgraded London Underground trains—at 75 dB; and 70-75 dB on the high-speed Ave railway in Spain. What are we in the US missing?).

Where inner and outer worlds meet: Synaptopathy

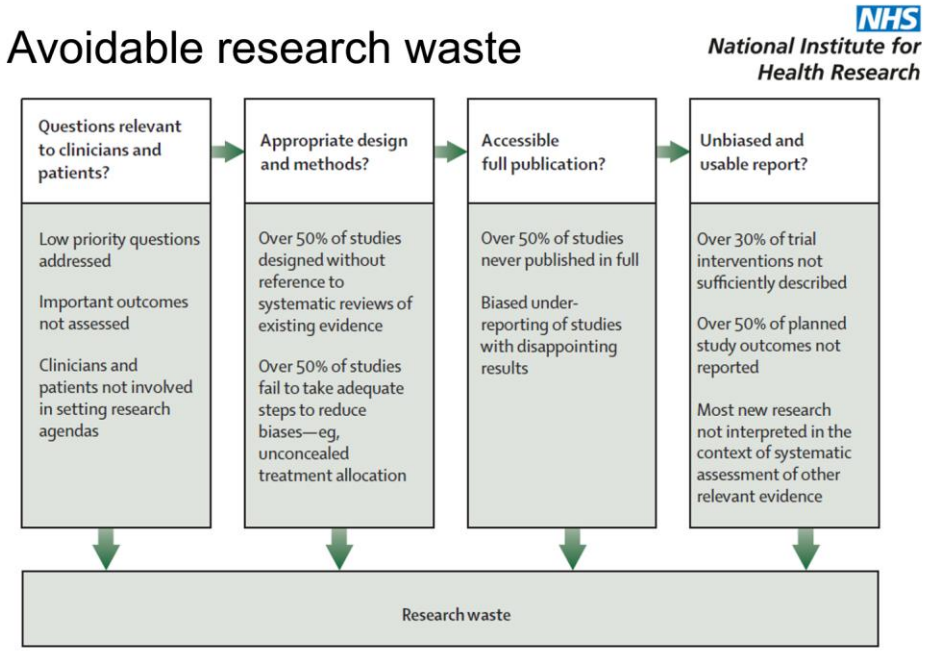
Several researchers presented on the place where hair cells and the first auditory neurons connect – the synapse. This synapse belongs to a nerve whose cell bodies form the cochlear nucleus—the first afferent waystation enroute to higher central centers. Disorders of synapses are known as *synaptopathies*. A pair of presentations focused on cochlear synaptopathy.

Michele Valero and Charles Liberman[29] noted that cochlear synaptopathy is a key contributor to hearing problems that result from ageing, noise exposure or toxicity. However, humans usually don't notice hearing-related changes until 90% of cochlear nerve fibers are lost (chalk one up for biological robustness). A subset of cochlear nerve fibers—those with high thresholds and low spontaneous discharge rates (low-SR)—are most vulnerable to many kinds of damage and may be important drivers of the middle ear muscle reflex (MEMR), which helps protect the inner ear from noise damage by tightening and stiffening the eardrum.[30] This could form the basis of a test for early cochlear synaptopathy. Using an elegant mouse model, the researchers could distinguish activity in the afferent pathway (indicating synaptopathy) from the efferent pathway (indicating central inhibition), and concluded that the MEMR may be useful in early detection of cochlear nerve damage.

Michelle Valero, Jane Burton, Charles Liberman et al[31] presented another study on cochlear synaptopathy, this time using various levels of sound exposure in anesthetized macaque monkeys. They found that synapses on IHCs (which connect with Type I neurons) were damaged at lower sound levels than those on OHCs (which connect with Type II neurons, thought to mediate pain hyperacusis): "...suggesting that synapses are the most vulnerable element in noise-exposed and ageing primates. Variations in the severity of synaptopathy may explain why two individuals with the same audiogram can have widely divergent performance on speech-to-noise tests." **I wonder how** the recent elegant work on cochlear synaptopathies, variability in distribution in the quantity and distribution of injury and interactions with the cause of hyperacusis and background environment and genetics will give rise to early detection and prevention or amelioration of this devastating condition.

A call for reducing 'avoidable research waste' and empowering the stakeholders

At the Next Steps event, **Deborah Hall**[32] presented on reducing 'research waste.' (See Bryan Pollard's article for details). Her framework fits in well with an all-stakeholders-determined research agenda, and will inform the now-established Hyperacusis Alliance's work. What is the most effective role for patients and their close associates in prioritizing research topics, and ensuring that outcomes that matter to patients as well as scientists and clinicians are addressed?



Chalmers & Glasziou Lancet 2009: 374:86-89
***http://www.thelancet.com/series/research* : January 2014**

[1] According to the Health Information and Management Systems Society, "Medical informatics is the interdisciplinary study of the design, development, adoption and application of information-technology-based innovations in healthcare services delivery, management and planning." (www.himss.org). I think of medical informatics as the science—and art—of transforming data to information to knowledge and understanding with the overarching goal of improving health outcomes for patients and society

[2] Health economics strives to quantify the economic consequences of health care decisions, interventions and programs. The consequences may be quantified from various perspectives, e.g. patient, society, employers or payers/insurers.

[3] However, Douglas Adams' *The Hitchhikers' Guide to the Galaxy* offers a humorous 'alternative viewpoint' on the role of lab mice

[4] However, a July 6, 2017 search at ClinVar—a widely-used database of studies that associate genetic variations with physical characteristics—shows no findings related to hyperacusis. ClinVar does, however, report several genetic associations with neuropathic pain (see 2016 ARO summary for more on hyperacusis pain).

[5] Typically, hyperacusis is diagnosed and quantified by the audiograms, which use a range of pure-tone frequencies to measure discomfort thresholds as loudness discomfort levels (LDLs). However, LDLs may not be completely reproducible between observers or on different days, and don't get at a common phenomenon—far lower thresholds for sounds of certain qualities such as those from rustling paper, machines or hammering. Pure tones are rare in our daily environment.

[6] Primary prevention: Steps to avoid acquiring a disease or condition that doesn't yet exist; secondary prevention: Steps to avoid worsening a disease the patient already has, including its complications. Screening: Detecting a disease or condition that isn't currently symptomatic or which has symptoms of which a person is not aware (for example a person with very mild hyperacusis might simply avoid noisy situations or not consider that their sound sensitivity is something to be concerned about)

[7] At the ARO dinner meeting, Heidi Nakajima (Assistant Professor of Otolaryngology) and Xiying Guan (Postdoctoral Research Fellow) of Harvard Medical School's Department of Otolaryngology presented on hyperacusis due to superior canal dehiscence (SCD), noting that the condition's prevalence in imaging and tissue studies is 0.5% to 1.9%, and that 30% of patients with SCD confirmed by CT scans had hyperacusis. It's not possible to translate these figures to the actual prevalence of SCD-related hyperacusis because patients who had CT scans presented because they had symptoms (in other words, many people may have SCD with no clinical symptoms) – but if most people who have SCD do eventually develop symptoms then SCD-related hyperacusis may be more common than we thought! Xiying calculated that if the prevalence of symptomatic SCD = 0.5% and 30% with symptomatic SCD also have hyperacusis, then if the US population is 325 million, nearly half a million people in the US have SCD-related hyperacusis.

[8] Of the University of Pennsylvania

[9] Variously of Draper, the Eaton-Peabody Laboratories of the Massachusetts Eye and Ear infirmary, and the Department of Otology and Otolaryngology at Harvard Medical School.

[10] Of the National Institute on Deafness and Other Communication Disorders

[11] Want more about the ECM? See http://jcs.biologists.org/content/123/24/4195.

[12] Variously of the University of Minnesota Department of Otolaryngology, Uppsala (Sweden) University Hospital Department of Surgical Sciences, Section of Otolaryngology

[13] For example, see https://ghr.nlm.nih.gov/gene/TNXB for a discussion of tenascin, a key protein component of the ECM

[14] Of the Department of Otolaryngology, Harvard Medical School & Massachusetts Eye & Ear (Boston, MA) and the Eaton-Peabody Laboratory, Massachusetts Eye & Ear Infirmary, Department of Otology and Otolaryngology, Harvard Medical School—Speech and Hearing Bioscience and Technology Program (at Harvard and MIT)

[15] Bradley Professor of Otolaryngology Head and Neck Surgery at Johns Hopkins School of Medicine, Baltimore, Maryland

[16] From the Center for Hearing and Deafness at the University of Buffalo (New York)

[17] Of the University of Tubingen, Department of Otolaryngology, Tubingen Hearing Research Center, Molecular Physiology of Hearing

[18] Wei Sun, Binbin Xiong, Senthilvelan Manohar, Guang-Di Chen and Richard Salvi variously from the University at Buffalo (New York) and the Center for Hearing and Deafness, Department of Communicative Disorders and Science, State University of New York at Buffalo
[19] From the Richard Salvi Center for Hearing & Deafness, Department of Communicative Disorders and Science, State University of New York at Buffalo
[20] Neuroscience Online, http://neuroscience.uth.tmc.edu/s4/chapter06.html. Accessed July 3, 2017.
[21] Variously of the School of Physics and Astronomy, University of Nottingham. NIHR Nottingham Hearing Biomedical Research Unit and the Manchester Centre for Audiology and Deafness, University of Manchester
[22] Siemens: QuietSuite (https://usa.healthcare.siemens.com/magnetic-resonance-imaging/mr-quiet); GE: Silent Works MRI (http://www3.gehealthcare.com/en/products/categories/magnetic_resonance_imaging/silent_scan). Toshiba: Vantage MRI with pianissimo (https://medical.toshiba.com/products/magnetic-resonance/vantage-titan-3t/).
[23] Director, Center for Hearing and Deafness at the University of Buffalo (New York)
[24] Massachusetts Eye and Ear Infirmary Harvard Medical School; Eaton-Peabody Laboratories, Massachusetts Eye and Ear Infirmary
[25] Wayne State University
[26] Variously of the University of Tübingen, Department of Otolaryngology, Tübingen Hearing Research Centre, Molecular Physiology of Hearing; Interfakultäres Institut für Biochemie, University of Tübingen; University of Bochum, Department of Pharmacology and Toxicology; and University of Würzburg, Department of Physiology
[27] University at Buffalo; Center for Hearing & Deafness, Department of Communicative Disorders and Science, State University of New York at Buffalo
[28] Noise help at http://www.noisehelp.com/noise-level-chart.html.
[29] Massachusetts Eye and Ear Infirmary, Harvard Medical School (Boston, MA)
[30] Valero MD, Hancock KE, Liberman MC. The middle ear muscle reflex in the diagnosis of cochlear neuropathy. Hearing Research 2016;332:29-38.
[31] Variously from *the Massachusetts Eye and Ear Infirmary, Harvard Medical School; Vanderbilt University; and the University of California at Davis*
[32] From the Nottingham Hearing Biomedical Research Unit at the University of Nottingham (England)