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Overview: Hearing loss, tinnitus, hyperacusis, and the role of central gain

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INTRODUCTION

Sensory hair cells in the cochlea transduce environmental sounds into driven high-fidelity neural signals that are conveyed by auditory nerve fibers to structures in the central auditory pathway. Auditory nerve fibers also exhibit distinctive rates of spontaneous activity in quiet that are among the highest rates of spontaneous activity observed in the adult mammalian nervous system. These inputs from the cochlea to central auditory pathways guide normal auditory brain development and are essential for normal auditory perception. Neuroscience studies have shown that when input from the cochlea to the brain is reduced by deafferentation arising from noise exposure, ototoxic drugs, or the aging process, forms of neural plasticity are enabled in central auditory structures that compensate for the missing input, but at some cost. Weak cochlear signals are progressively amplified along the auditory pathway, yielding larger responses than normal (increased central gain), altered tuning bandwidths, and increased spontaneous and synchronous neural activity, which may contribute in varying degrees to tinnitus, hyperacusis, and difficulties in normal listening (Eggermont and Roberts, 2014).

Over the past decade, it has become clear that injuries to cochlear hair cells (Lobarinas et al., 2013; Landegger et al., 2016) or to afferent synapses on inner hair cells (Kujawa and Liberman, 2009) may not be sufficient to elevate thresholds for the detection of sound in quiet, which are measured by the standard clinical audiogram. The articles of this special issue discuss (1) how different cochlear structures are affected by noise exposure, ototoxic drugs, and aging, and (2) and how these changes may be detected by non-invasive methods more sensitive than simple, pure tone threshold measures. Other articles describe (3) how the input/output (I/O) functions of neurons change after hearing loss and how these changes are expressed in neural and behavioral responses. A final topic (4) considers whether changes in central gain are sufficient to explain tinnitus, hyperacusis, and subtle hearing impairments, or whether further research is needed to account for these phenomena. Results are drawn from animal models of tinnitus and hearing loss as well as from studies in which the sound environment is artificially diminished or augmented in humans and animals.

The aim of the special issue is not to present overarching reviews of these topics (for reviews, see Eggermont and Roberts, 2014; Shore et al., 2016; Liberman and Kujawa, 2017) but to highlight current issues and discuss directions that emerge from consideration of the articles reported in the issue (these articles cited in italics below).

COCHLEAR SYNAPATOPATHY IN ANIMAL MODELS

Aging and noise exposure affect several aspects of cochlear function including the density and integrity of outer (OHC) and inner (IHC) hair cells, ribbon synapses on IHCs, and the survival of auditory nerve fibers (ANFs) that relay information from the IHCs to the spiral ganglion and to the cochlear nucleus. In this section, the focus is mainly on pre- and post-synaptic elements of ribbon synapses, which are particularly vulnerable to damage by noise exposure and if lost may impair suprathreshold auditory processing when hearing thresholds are normal.

In their initial report, Kujawa and Liberman (2009) found that noise trauma that produced only a temporary threshold shift in a mouse model was nonetheless sufficient to destroy up to ~50% of afferent synapses on IHCs followed by a progressive loss of spiral ganglion (SG) cell bodies over the lifespan. The synaptic loss also accelerated the rate of age-related neural loss compared to that seen in unexposed animals. In this issue, Wu et al. (2019) examine measures of cochlear neuropathy related to age (0–89 years) in human temporal bones taken from cases with no history of otologic disease. OHC loss was 30–40% (0.25–8 kHz) in subjects over age 60, with comparatively greater losses at the low-frequency apical and high-frequency basal ends of the cochlea. IHC loss was rarely >10% at any age. However, neural loss (quantified as Type I ANF axon loss) greatly exceeded IHC loss, with subjects over 60 years of age showing 60% loss of peripheral axons relative to the youngest subjects. The slope of axon loss to age-related loss of IHCs was almost 3:1. The results suggested that a large number of auditory neurons in the aging ear are disconnected from their hair cell targets. Primary neural degeneration on this scale may not affect the audiogram but likely would contribute to age-related hearing impairment, especially in noisy environments.

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In a related paper, Parthasarathy et al. (2019) describe how age-related loss of afferent synapses connecting auditory nerve fibers to IHCs (synaptopathy) in animals is accompanied by degraded neural coding of temporal envelope cues at the auditory periphery. This neuronal loss is accompanied by increases in the temporal representation of lower-frequency modulations in the central pathway that are likely re-shaped by decreased inhibitory transmission across the various auditory nuclei. Altered representations of different temporal modulations in speech at multiple levels of the pathway may contribute to the well-known decline in age-related changes in speech perception, particularly noticeable in noisy environments.

An emerging question of considerable importance is whether synaptopathy and neural degeneration can be prevented. In a study of noise-induced cochlear synaptopathy, Altschuler et al. (2019) measured the ability of rats that had previously been exposed to simulated small arms fire to detect silent gaps embedded in background noise. Noise exposure reduced synaptic ribbon counts by 40% with minimal OHC loss. Synaptic losses were greater in the noise-exposed animals that were deficient at detecting silent gaps in background sound. These results suggested that tinnitus may have filled in the silent gaps or alternatively that temporal resolution was impaired by the synaptic loss. Pretreatment of the animals with drugs known to reduce excitotoxicity significantly reduced the incidence of synaptopathy. Surprisingly, however, pretreatment did not significantly prevent deficits in gap detection caused by noise exposure.

While these results suggest that it may be possible to protect cochlear synapses from the damaging effects of traumatic noise by pretreatment with anti-excitotoxic drugs, it is presently debated whether synapses once damaged can be repaired. Chen et al. (2019) discuss their findings regarding this controversial issue. Suzuki et al. (2016) found that delivery of the neurotrophic factor NT-3 to the round window of mice within 24 h of noise exposure regenerated IHC ribbon synapses and increased the amplitude of wave 1 of the auditory brainstem response (ABR). Because NT-3 is highly expressed in the cochlea of several rodent species over the lifespan, it might conceivably support an intrinsic repair process over a longer time. Chen et al. (2019) conclude from their studies in guinea pigs that synapses damaged by a single traumatic noise exposure can be partially repaired, but the repaired synapses are functionally abnormal. This contrasts with evidence in mice (Kujawa and Liberman, 2009) where a progressive decline in synaptic counts attended by a loss of SG cell bodies was observed over several weeks with no evidence of recovery after noise exposure. At issue with respect to the recovery of damaged ribbon synapses are possible species differences, the time course of study, and methodological challenges in immunolabeling and in confocal and fluorescent imaging of pre- and post-structures at the base of the IHC. Future studies quantifying SG cell bodies over time in different species may help to resolve this issue, which has important implications for hearing health.

NONINVASIVE MEASUREMENT OF SYNAPTOPATHY

Other articles in the special issue address whether synaptopathy can be detected noninvasively in humans. The ribbon synapses and ANFs most vulnerable to damage by noise exposure are those exhibiting low rates of spontaneous activity (LSR ANFs) and high thresholds for firing, with LSR ANFs tuned to high frequencies being particularly vulnerable (Furman et al., 2013). Because LSR fibers fire only to suprathreshold sounds at intensities well into the speech range and are resistant to saturation by background noise, they may be especially important for temporal processing of speech in noisy environments. Temporal coding abilities measured by different methods are therefore potential candidates for detecting synaptopathy in humans.

In their article also discussed above, Parthasarathy et al. (2019) describe how envelope following responses (EFRs) can be used to assess changes in temporal processing abilities and synaptopathy related to aging. EFRs are electrophysiological responses recorded by EEG and evoked by tones amplitude modulated (AM) at frequencies near 85 Hz and above. EFRs evoked by stimuli AM between 80 and 100 Hz in humans are generated by sources in the auditory midbrain, while EFRs evoked at modulation rates near 1000 Hz in animals (this rate a technical challenge in humans) originate from the auditory nerve (Shaheen et al., 2015). EFRs are preferentially sensitive to LSR ANF synaptopathy at these modulation rates because LSR ANFs show greater synchronization to sound modulations at these rates than do HSR fibers, particularly at shallow modulation depths and moderate to high sound levels where HSR fibers typically saturate. EFRs recorded with suitable methods are therefore potential candidates for noninvasive detection of synaptopathy. In support of this principle, EFRs evoked by sounds AM at 1024 Hz are sensitive to verified noise-induced synaptopathy (Shaheen et al., 2015) and correlate with age-related synaptic losses (Parthasarathy and Kujawa, 2018) in mouse models. Other provocative results have been reported in studies relating behavioral temporal processing abilities to EFRs evoked at AM rates of ~100 Hz in normal hearing humans (Bharadwaj et al., 2015) and in subjects with tinnitus and their controls both with audiometrically normal hearing (Roberts et al., 2018), but not all results agree (Guest et al., 2017).

In this issue, Bharadwaj et al. (2019) point out that because EFRs can be affected by factors other than synaptopathy, their application and interpretation in humans are not straightforward. Through a series of experiments, six extraneous factors were examined that can affect EFRs as well as other candidate measures of synaptopathy (ABRs, acoustic reflexes). Using strategies to mitigate the extraneous effects, Bharadwaj et al. (2019) found three suprathreshold physiological assays that exhibited across-individual correlations with each other, which may be indicative of contributions arising from a common physiological source consistent with hidden cochlear synaptopathy. Notably, thresholds elevated in the 8–16-kHz range (these thresholds indicating OHC damage)

were significantly associated with reduced click-evoked ABR wave I amplitudes. This suggests that cochlear synaptopathy co-occurs with damage to OHCs in the high-frequency base of the cochlea. Because clinical audiograms only assess hearing from 0.25 to 8 kHz, clinicians and scientists need to consider hearing loss in the ultra-high frequency range (9–16 kHz). Indeed, many tinnitus patients have normal clinical audiograms, but often have undetected hearing loss at the ultra-high frequencies, where their tinnitus frequencies also localize (Roberts et al., 2006, 2008; Knudson and Melcher, 2016).

Another step toward noninvasive measurement of synaptopathy by EFRs is described by Wang et al. (2019). These authors report that simultaneous presentation of multiple complex tones with different fundamental frequencies leads to repeatable measures of temporal coding fidelity of the sound envelope (a type of EFR) recorded from the cochlear frequency regions corresponding to the narrowband carrier frequencies. The correspondence of spectral peaks between single and concurrent presentations was good, although some small differences were detected in overall EFR amplitude evoked by the single band compared to the multiband stimuli. Off-frequency contributions to the EFRs produced by spread of masking were noted, but were minimal compared to on-band responses. The findings suggest the utility of using multi-band complex tone stimuli to estimate the profile of temporal coding fidelity and thus potentially the degree of synaptopathy or other sources of hidden hearing loss a function of cochlear place.

Another promising non-invasive measure of synaptopathy is the middle ear muscle reflex (MEMR), also known as the stapedius reflex or acoustic reflex. The MEMR is measured as the change in middle-ear immittance induced by sound-driven efferent feedback from the middle-ear muscles. Physiological studies indicate that high-threshold LSR ANFs dominate among inputs to the MEMR circuit, which suggests that the MEMR may be a sensitive measure of synaptic loss affecting these fibers (Valero et al., 2018). MEMR amplitudes have also been reported to be reduced in tinnitus patients with normal audiograms compared to controls (Wojtczak et al., 2017) where hidden hearing loss has been suspected. However, in this issue, Guest et al. (2019) were unable to confirm a relationship of MEMR thresholds to tinnitus in a sample of 19 patients compared to an equal number of controls without tinnitus, all of whom had normal clinical audiograms. Several factors discussed by Guest et al. (2019) may affect such results including the age of the participants, how tinnitus is defined, and how the MEMR is measured.

In a final article in this group, Huet et al. (2019) report that high-spontaneous rate (HSR) fibers driven by low-frequency tones in noise are able to phase lock 30 dB below the level that evoked a significant elevation of the discharge rate, whereas LSR fibers switch their preferential mode of coding from rate in quiet to time (phase) in noise. A new diagnostic metric is proposed for animal studies that utilizes recordings from the round window. The metric is shown to be sensitive to loss of LSR fibers with high-frequency tuning following application ouabain, which selectively eliminates neural responses of these fibers to sound without affecting OHCs.

HYPERACUSIS, TINNITUS, AND CENTRAL GAIN

A third group of articles in the special issue examines neural changes induced by administration of salicylate or noise exposure, which cause hearing loss. Although the hearing loss induced by these methods is usually temporary (noise exposure can be titrated to avoid permanent threshold shifts), noise exposure has been reported to cause synaptopathy in the high frequency region of the cochlea despite threshold recovery (Heeringa et al., 2018). Salicylate and noise trauma also induce tinnitus and hyperacusis behavior in animals, as assessed putatively by several behavioral methods. A major question addressed here is whether the relationship of the neural and behavioral changes to one another is consistent with the central gain hypothesis of hyperacusis.

Auerbach et al. (2019) note that the procedures used to induce hyperacusis and tinnitus in animal models can have effects in the brain beyond those of deafferentation and hearing loss. For example, systemic administration of salicylate (the manipulation they use) increases neural excitability throughout the brain in addition to acutely disrupting neural output from the cochlea to the central auditory pathway. Neural changes and behavioral changes could in principle reflect either or both of these effects. To more precisely determine the relationship of behavioral and neural changes, Auerbach et al. concurrently measured behavioral responses elicited by sounds of increasing intensity and neural responses recorded from the inferior colliculus (IC) and auditory cortex (AC) of unanesthetized rats before and 2 h after salicylate administration. At low sound intensities, salicylate reduced behavioral and neural responses compared to baseline, an effect likely reflecting acute cochlear hearing impairment, but at higher sound intensities, both responses exceeded baseline putatively reflecting hyperacusis. These results were obtained in the IC as well as in the AC but were somewhat stronger in the AC, suggesting accelerating gain at higher levels of the pathway. The findings suggest that hyperacusis likely reflects changes neuronal gain that aggregate simultaneously at multiple levels of the auditory system.

Although it should be noted that changes in excitatory and inhibitory drive consequent on diminished input from the auditory nerve might directly alter the balance of excitation and inhibition in central auditory structures, homeostatic plasticity mechanisms operating at different levels of the pathway may also be involved and would be expected to express their activity over time. Consistent with this hypothesis, Chambers et al. (2016) found that loudness growth functions based on neural firing rate recovered progressively to normal levels in the AC, and to a lesser extent in the IC, over an interval of 7 to 30 days after permanent unilateral deafferentation of the auditory nerve by ouabain in mice. Because no measurable ABR response was recorded from the auditory nerve over this time, it was concluded that homeostatic plasticity mechanisms were engaged. In this issue, Balaram et al. (2019) quantified mRNA levels for genes encoding AMPA and $GABA_A$ receptor subunits in single neurons in the IC and AC 30 days after unilateral hearing loss caused by ouabain infusion. Expression of mRNA coding for AMPA receptor subunits was significantly increased, while mRNA coding for

$GABA_A$ subunits was significantly decreased on the affected side. As reported by Chambers et al. (2016) and by Auerbach et al. (2019) in this issue, neural changes were observed in AC as well as IC but were more pronounced in AC. Balaram et al. (2019) propose that opposing transcriptional shifts in AMPA and GABA receptor genes observed several weeks after a peripheral insult may act cooperatively to support a homeostatic recovery of neural activity following auditory deprivation.

Evidence for reciprocal homeostatic plasticity mechanisms yielding positive and negative shifts in central gain is described by Pienkowski (2019) and by Sheppard et al. (2019) in this issue. Pienkowski (2019) reviews evidence that immersive exposure to moderate level background sounds in humans attenuates the perceived loudness of sound stimuli, while artificial sound attenuation has the opposite effect, i.e., increasing perceived loudness. These observations are congruent with Pienkowski's findings that passive sound exposure in cats for several weeks suppressed neural responsiveness for the exposure frequencies while off-band responsiveness was enhanced, presumably reflecting a loss of lateral suppression from the on-band region (Pienkowski et al., 2011). These and other experimental studies reviewed by Pienkowski provide a basis for therapeutic interventions for hyperacusis and for tinnitus. Although the literature on clinical interventions is large and positive findings have been reported, Pienkowski notes that well controlled studies are lacking. Sheppard et al. (2019) exposed rats to 12 h of low-level noise either in the light or dark phase of the circadian cycle for 5 weeks. Contrary to earlier studies which reported that the effect of traumatic noise on cochlear function depended on the circadian cycle, cochlear function (measured by distortion product otoacoustic emissions and the compound action potential) was not affected by the light–dark cycle. However, neural activity in the IC demonstrated negative gain in a frequency and intensity specific manner compared to unexposed controls in both cycles.

Möhrle et al. (2019) explored the relationship of changes in central gain to tinnitus in an animal model of both conditions. Following the model of Zeng (2013), the authors modified their earlier operant behavioral test for tinnitus in rats to provide a behavioral loudness growth function as well as an index of tinnitus. Noise-exposed rats were then divided into four groups showing either no sign of tinnitus or hyperacusis, one or the other of these conditions, or both conditions. In addition, neural loudness growth was measured as the ratio of the sound-evoked ABR wave V to ABR wave I. A surprising result was that animals expressing tinnitus exhibited a decrease in the V/I ratio (a putative decrease in neural loudness growth) after noise exposure compared to animals in the other groupings. This observation is congruent with findings reported earlier by this research group (Singer et al., 2013) which suggested that a *failure* to mobilize neural plasticity genes eventuated in tinnitus. Effects of tinnitus on ABR wave I and V latency and in functional connectivity in the AC assessed by resting state fMRI were also reported. Because similar changes were seen in human tinnitus sufferers compared to controls, Möhrle et al. (2019) suggest that further development of these methods may yield a biomarker for tinnitus (a goal that has proven elusive in the tinnitus field).

Procedures such as salicylate and noise exposure steepen neural and behavioral loudness growth functions, suggesting the presence of hyperacusis. However, tinnitus is also expected as a consequence of these procedures, since input from the auditory nerve is typically reduced. In contrast to driven responses reflecting hyperacusis, Martel et al. (2019) investigated changes in the spontaneous and synchronous activity of fusiform cells in the dorsal cochlear nucleus (DCN) of guinea pigs, and in the timing rules of stimulus-timing-dependent neural plasticity (STDP) in this structure, following administration of a salicylate dose expected to produce tinnitus behavior. This research group has extensively characterized such neural changes in previous research using noise trauma (Wu et al., 2016; Marks et al., 2018) giving a baseline for comparison. In addition, Martel et al. (2019) assessed tinnitus by the gap-startle method as in their previous research as well as by an operant method in which a tinnitus-like sound was made a signal for a behavioral response. Martel et al. (2019) found that salicylate produced tinnitus assessed by both behavioral methods that was indistinguishable in terms of prevalence and frequency profile from that observed previously in their studies of noise exposure. The effects of salicylate and noise exposure on neural responses were also highly similar. After salicylate treatment, spontaneous and synchronous neural activity increased in the DCN of animals expressing tinnitus compared to animals that did not, and the timing rules of STDP shifted toward potentiation specifically in these animals. These findings suggest that the neural mechanisms underlying tinnitus behavior may be similar for salicylate and noise exposure. It may be relevant that the noise trauma used by this research group is titrated from baseline research to give temporary, not permanent, hearing threshold shifts in guinea pigs, and the amplitude of startle responses is typically not changed. These features might remove the potentially confounding effects of hyperacusis to tinnitus and neural measurement.

In a final paper in this group, Lauer et al. (2019) note that hidden hearing loss could be an important factor in children otherwise diagnosed with auditory processing disorder. Lauer et al. review how abnormal acoustic activity early in life (increased or decreased activity) can lead to synaptic and structural changes in the auditory brainstem. They also note that in trying to understand the mechanisms underlying central auditory gain, control of cochlear gain via the olivocochlear pathway should also be considered. It has been suggested that some of the inter-subject variability in vulnerability to age-related hearing loss, tinnitus, and sound level tolerance may arise from individual differences in the strength of the sound-evoked medial olivocochlear reflex. This pathway has been reported to be hypersensitive in tinnitus patients and may play a modulating role in both conditions (Knudson et al., 2014). Other studies have shown than unilateral removal of the tympanic membrane or transection of olivocochlear bundle in young adult mice is followed in adult life by a loss of lateral olivocochlear efferents projecting to IHC synapses and is accompanied by synaptopathy and elevated ABR thresholds on the ipsilateral side (Liberman et al., 2015).

Such changes induced by deafferentation represent another mechanism that may contribute to neural changes in hearing loss. In sum, Lauer et al. (2019) note that even moderate changes in acoustically driven activity can have measurable effects in auditory afferent and efferent pathways, and some of these effects may contribute to changes in hearing behavior.

IS CENTRAL GAIN SUFFICIENT FOR TINNITUS?

The occurrence of tinnitus is associated with hearing loss and neuroplastic changes in the brain. However, disentangling the relationship of both of these changes to tinnitus and to its frequent comorbid symptom hyperacusis has remained elusive in both human and animal studies. Brotherton et al. (2019) used earplugs to impose a period of monaural deprivation and induce a temporary, reversible tinnitus in normal hearing human subjects. The goal was to test whether differences in subcortical changes in neural gain measured by changes in acoustic reflex thresholds (ARTs) could explain the occurrence of tinnitus. Of 44 subjects who wore an earplug in one ear for either 4 or 7 days, 30 subjects reported tinnitus at the end of the deprivation period. ARTs were measured before the period of earplug insertion and immediately after earplug removal. At the end of the earplug period (4 days or 7 days), ARTs in the plugged ear were significantly decreased by 5.9 dB in the tinnitus-positive group, but also by 6.3 dB in the tinnitus-negative group. Thus, neural changes sufficient to increase central gain were present in the tinnitus group, but these changes by themselves were not sufficient to generate a tinnitus sensation in the no-tinnitus group. In the control ear, ARTs increased slightly 1.3 dB in the tinnitus-positive group and by 1.6 dB in the tinnitus-negative group, reflecting small a decrease in gain possibly compensatory to gain increases on the contralateral side. Brotherton et al. (2019) suggested either that the subcortical neurophysiological changes underlying the ART reductions might not be related to tinnitus or that they may be a necessary component but additional changes at a higher level of auditory processing are required to generate tinnitus percepts.

One such higher-order process may be mechanisms that support attention, which have been reported to be altered in human tinnitus sufferers (reviewed by Roberts et al., 2013). Brozoski et al. (2019) examined the effect of tinnitus on vigilant and selective auditory attention in rats previously exposed to unilateral noise trauma expected to induce tinnitus. Tinnitus was diagnosed when the noise-exposed rats failed to discriminate their putative tinnitus from external sounds that covered the expected tinnitus frequency region. Tinnitus animals were more vigilant (responded more quickly to a tone signaling food availability) than non-tinnitus animals or unexposed controls when the signaling tone was in the tinnitus frequency region. In contrast, the tinnitus group performed more poorly on a task of selective attention in which a train of sound pulses signaled a left or right nose-poke. Although noise exposure elevated ABR thresholds by about 20 dB in the exposed ear, the extent these shifts did not differ between the tinnitus and non-tinnitus groups, and thresholds in the unexposed ear were normal. Thus, as has been reported in human studies, Brozoski et al. (2019) suggested that animals with chronic trauma-induced tinnitus have their attention at least partially bound to their tinnitus.

How this binding may work is discussed by Sedley (2019) in the last article of the special issue. This article reviews neural and behavioral manifestations of central gain, techniques for its measurement, and the multiple neural mechanisms by which gain changes can occur in the auditory pathway after tinnitus-inducing procedures. Sedley (2019) concludes that there is compelling evidence that peripheral auditory insults cause changes in neuronal firing rates, neural synchrony, and neurochemistry signifying an increase in central gain. However, while these changes are sufficient to distinguish groups of animals exhibiting tinnitus from control groups that do not, the changes do not necessarily predict tinnitus behavior at the level of individual subjects. Sedley (2019) reconciles the findings by suggesting that additional mechanisms contribute to the generation of tinnitus. One of these mechanisms may be neuromodulatory attention systems that appear to be engaged in tinnitus and are thought to support higher-level perceptual functions that are necessary for the conscious experience of tinnitus. Such mechanisms are activated by signals in proportion to their magnitude relayed from subcortical pathways, whether those signals be veridical as is the case when the sensory epithelium encounters an adequate stimulus, or phantom signals, such as the case of hypersynchronous neural activity generated by homeostatic and STDP plasticity mechanisms operating in hearing loss (Sedley et al., 2016). Signals of both types may be modulated by changes in central gain, making gain changes relevant to tinnitus as well as to hyperacusis. Engagement of higher-order mechanisms may be necessary to identify phantom signals inherited from the auditory pathway as auditory objects.

CONCLUSION: LOOKING AHEAD

This overview reveals a need for qualifications. For example, increased central gain may upregulate brain stem sources that contribute to EFRs in humans, diminishing the sensitivity of EFRs to synaptic losses that might potentially differentiate tinnitus and control subjects. Measures more directly dependent on activity in the auditory nerve are desirable. Efferent hypersensitivity which has been reported in tinnitus is another variable that may obscure the role of cochlear pathology in tinnitus and altered sound level tolerance. Animal models of tinnitus and hyperacusis have a distinct advantage in examining such questions, but their validity has been questioned with regard to distinguishing behavioral changes due to hearing loss, impaired temporal processing, or hyperacusis from those dependent on the presence of a phantom sound. More detailed assessment of cochlear function and cross validation of findings from different methods may verify the picture described above.

Some further topics of note were not explicitly addressed in special issue. A robust finding in humans and animals is that

some subjects develop tinnitus and reduced sound level tolerance after exposure to loud noise or other known tinnitus triggers while other subjects do not. What are the sources of resilience among those subjects that do not develop tinnitus or hyperacusis, even though hearing loss may be present? Genetic factors and the role of the olivocochlear efferents are beginning to attract further research interest. Another question is posed by a large literature which shows that tinnitus neural activity is not confined to auditory pathways but is widely distributed in the human brain. Much of this activity is expressed as low frequency cortical oscillations that may reflect integration of tinnitus-related activity in the auditory pathway with information in other brain regions. Such distributed activity may be involved in normal auditory processing into which tinnitus may provide some insight.

A third question enquires into the role of the spontaneous activity of the auditory nerve in tinnitus. Recent cochlear modeling of EFRs recorded in quiet and in background noise from human tinnitus and control subjects with normal audiograms found that while synaptopathy affecting LSR ANFs was sufficient to explain the relationship of EFRs to temporal processing performance in the control subjects, a further loss of HSR ANFs fibers hidden from the audiogram was needed to explain this relationship in the tinnitus group (Paul et al., 2017; Roberts et al., 2018). HSR synaptopathy appeared to add tinnitus to deficient temporal processing which was observed in the tinnitus subjects. A key role for HSR fibers (the health of which is tapped by the clinical audiogram) in tinnitus is also consistent with the observation that 85% or more of adult human tinnitus sufferers exhibit explicit audiometric hearing loss. Why might HSR fiber synaptopathy be a key factor in tinnitus? The answer may be that the high rates of spontaneous activity of these ANFs in quiet drives narrow and wide band inhibition in the CN where tinnitus signals are first generated (Wu et al., 2016). That inhibition may gate STDP plasticity in the normal CN such that its reduction by hearing loss not only enables homeostatic changes that give rise to hyperacusis, but also unleashes STDP in this multisensory structure yielding hypersynchronous activity that is identified by higher centers as a tinnitus signal. Studies comparing the spontaneous activity of the auditory nerve between animals expressing and not expressing behavioral evidence of tinnitus after noise exposure or salicylate may be informative.

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