Veterans Review and Appeal Board

Hearing Exhibits & Attachments List

BPA SUBMISSION ON NEW 2025 HEARING LOSS GUIDELINES

Exhibits

Ex-1: Liberman, M. C., & Kujawa, S. G. (2017). Cochlear synaptopathy in acquired sensorineural hearing loss: Manifestations and mechanisms. *Hearing Research, 349*, 138–147. (10 pages)

Ex-2 : Rutka, J. (2010). *Discussion Paper on Hearing Loss (*updated December 2011), pp. 11, 13-14, 17, 31-32. (7 pages)

Ex-3: Government of Canada. (2024). *Noise and sound: Hearing loss and tinnitus.* (10 pages)

Ex-4: Merck Manual – Professional Version. (2024). *Hearing Loss.* (27 pages)

Ex-5: Yong, J. S., & Wang, D. (2015). Impact of noise on hearing in the military. *Military Medical Research, 2*(1), 6. (6 pages)

Ex-6: Liberman, M. C., & Kujawa, S. G. (2009). Adding insult to injury: Cochlear nerve degeneration after 'temporary' noise-induced hearing loss. *The Journal of Neuroscience*, 29(45), 14077–14085. (9 pages)

Ex-7: Liberman, M. C. (2017) Noise-induced and age-related hearing loss: new perspectives and potential therapies. *F1000Research* 6(F1000 Faculty Rev),927. (11 pages)

Ex-8: Liberman, M. C., & Kujawa, S. G. (2006). Acceleration of age-related hearing loss by early noise exposure: evidence of a misspent youth. *The Journal of Neuroscience* 26(7),2115-2123. (9 pages)

Ex-9: Fernandez, K. A., Jeffers, P. W. C., Lall, K., Liberman, M. C., & Kujawa, S. G. (2015). Aging after noise exposure: Acceleration of cochlear synaptopathy in 'recovered' ears. *The Journal of Neuroscience*, 35(19), 7509–7520. (12 pages)

Ex-10: Yamasoba, T., Lin, F. R., Someya, S., Kashio, A., Sakamoto, T., & Kondo, K. (2013). Current concepts in age-related hearing loss: Epidemiology and mechanistic pathways. *Hearing Research, 303*, 30–38. (19 pages)

Ex-11: Fink, D. (2024). What is the safe noise level to prevent noise-induced hearing loss? *Journal of Exposure Science & Environmental Epidemiology 35*, 124-128 (5 pages)

Ex-12: Kohrman, D. C., Wan, G., Cassinotti, L., & Corfas, G. (2020). Hidden hearing loss: a disorder with multiple etiologies and mechanisms. *Cold Spring Harbor Perspectives in Medicine* (19 pages)

Ex-13: Bramhall, N. F., Konrad-Martin, D., McMillan, G. P., & Griest, S. E. (2017). Auditory brainstem response altered in humans with noise exposure despite normal outer hair cell function. *U.S. Department of Veterans Affairs* (27 pages)

Ex-14: Waddell, K., Wu, N., Demaio, P., Bain, T., Bhuiya, A., Wilson, M.G. (2024). Examining the association between noise exposure and delayed hearing loss. *McMaster University.* (4 pages)

Ex-15: Canadian Centre for Occupational Health and Safety. (2023). *Noise – occupational exposure limits in Canada* (9 pages)

Ex-16: Yankaskas, K. (2013). Prelude: noise-induced tinnitus and hearing loss in the military. *Hearing Research 295,* 3-9 (6 pages)

Ex-17: Gates, G. A., Schmid, P., Kujawa, S. G., Nam, B., & D'Agostino, R. (2000). Longitudinal threshold changes in older men with audiometric notches. *Hearing Research 141,* 220-228 (9 pages)

Ex-18: World Health Organization. (2021). *World report on hearing*. (12 pages)

Attachments

Attach-1: Cole v. Canada (A.G.), 2015 FCA 119 (CanLII), [2016] 1 FCR 173, paras 89-92, 97-99, 121 (40 pages)

Attach-2: Veterans Review and Appeal Board decision #100003937933 (10 pages)

Attach-3: Veterans Review and Appeal Board decision #100004407577 (4 pages)

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Review Article

Cochlear synaptopathy in acquired sensorineural hearing loss: Manifestations and mechanisms

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ABSTRACT

Common causes of hearing loss in humans - exposure to loud noise or ototoxic drugs and aging - often damage sensory hair cells, reflected as elevated thresholds on the clinical audiogram. Recent studies in animal models suggest, however, that well before this overt hearing loss can be seen, a more insidious, but likely more common, process is taking place that permanently interrupts synaptic communication between sensory inner hair cells and subsets of cochlear nerve fibers. The silencing of affected neurons alters auditory information processing, whether accompanied by threshold elevations or not, and is a likely contributor to a variety of perceptual abnormalities, including speech-in-noise difficulties, tinnitus and hyperacusis. Work described here will review structural and functional manifestations of this cochlear synaptopathy and will consider possible mechanisms underlying its appearance and progression in ears with and without traditional 'hearing loss' arising from several common causes in humans.

Contents

1. Overt vs. 'hidden' hearing loss

A longstanding view of acquired sensorineural hearing loss (SNHL) has been that cochlear hair cells are among the most vulnerable elements in the cochlea and that, in the vast majority of cases, cochlear nerve fibers degenerate if, and only long after, the loss of their peripheral hair cell targets. This view arose, fundamentally, because of the temporal offset between post-insult degeneration of hair cells and loss of the spiral ganglion cell (SGC) bodies of the primary auditory neurons with which they

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Abbreviations

ABR	Auditory Brainstem Response
AMPA	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid
ANF	Auditory Nerve Fiber
CAP	Compound Action Potential
CtBP2	C-terminal Binding Protein 2
DPOAE	Distortion Product Otoacoustic Emission
GLAST	Glutamate Aspartate Transporter
GluR	Glutamate Receptor
IHC	Inner Hair Cell
OHC	Outer Hair Cell
PTS	Permanent Threshold Shift
SGC	Spiral Ganglion Cell
SNHL	Sensorineural Hearing Loss
SPL	Sound Pressure Level
SR	Spontaneous Rate
TTS	Temporary Threshold Shift

communicate. In animal models exposed to noise or ototoxic drugs, hair cell loss can be widespread within hours (Bohne and Harding 2000; Lawner et al., 1997; Suzuki et al., 2008; Wang et al., 2002; Webster and Webster, 1978), whereas the loss of SGCs is typically not detectable for weeks to months after insult and can progress for years (Johnsson, 1974; Miller et al., 1997; Sugawara et al., 2005; Webster and Webster, 1978).

Threshold elevations accompany hair cell damage and loss; for human assessments, the behavioral pure tone audiogram is a key metric of this overt hearing loss, providing documentation of the magnitude of the audibility loss, its pattern as a function of frequency, and to some extent underlying site(s) of dysfunction (e.g. middle ear, inner ear). It has long been known, however, that audiometric thresholds do not always reflect reported or demonstrated auditory perceptual difficulties and that thresholds and otopathology are not always well aligned (Bharadwaj et al., 2015; Felder and Schrott-Fischer, 1995; Gordon-Salant, 2005; Grose and Mamo, 2010; Halpin et al., 1994; Moore, 2004; Lobarinas et al., 2013; Ruggles et al., 2011; Schuknecht and Gacek, 1993).

Recent work in animal models has shed new light on this disconnect. It is now clear, at least in the noise-exposed and aging ear, 1) that cochlear neurons are a primary target, 2) that their peripheral synaptic connections are the most vulnerable elements and 3) that cochlear nerve synapses can be destroyed even when hair cells survive. Although threshold shift is a sensitive metric of underlying hair cell damage, it is relatively insensitive to this diffuse loss of inner hair cell (IHC) synapses or of the cochlear nerve fibers they drive; indeed, behavioral detection thresholds for tones are little changed until neural loss exceeds about 80–90% (Schuknecht and Woellner, 1955). Thus, cochlear synaptopathy can be widespread in ears with intact hair cell populations and normal audiograms, where it has been called "hidden" hearing loss (Schaette and McAlpine, 2011).

This basic result has been observed in multiple mammalian species, including compelling preliminary observations in human temporal bones (Viana et al., 2015) and in noise-damage created by both continuous (Rybalko et al., 2015; Singer et al., 2013; Wang and Ren, 2012) and impulsive/blast exposures (Cho et al., 2013) and in ears with, and without permanent threshold shifts (Kujawa et al., 2011). Beyond noise and aging, gentamicin-treated mice (Ruan et al., 2014) and temporal bones of humans who received aminoglycosides in life (Hinojosa and Lerner, 1987; Sone et al., 1998) can display diffuse cochlear neuropathy for treatments not sufficient to cause hair cell loss. To date, findings have been most thoroughly described in mouse models of noise and aging, as discussed in the following sections.

2. Cochlear synaptopathy and neurodegeneration in noise-exposed and aging mice

In recent years, results of a study aiming to investigate whether noise can have delayed or progressive consequences in humans (Gates et al., 2000) motivated a series of experiments in an inbred strain of good-hearing, normally aging mice (CBA/CaJ), where intended exposures could be rigidly specified, unintended exposures avoided, and a variety of other potentially cofounding variables controlled in genetically ~ identical individuals. Mice were exposed at various ages and were held with age-matched controls for varying post-exposure times. Contrary to existing dogma, results demonstrated that noise can cause ongoing changes in cochlear structure and function long after it has ceased. An unanticipated finding of these initial studies was a dramatic loss of cochlear neurons as young-exposed animals aged after a noise exposure that produced moderate, permanent threshold shift (PTS), but no hair cell loss (Kujawa and Liberman, 2006).

To explore this finding of noise-induced primary neuropathy further, and to uncomplicate interpretation, the observations were repeated for an exposure that produced only temporary threshold shift (TTS) in fully adult animals (Kujawa and Liberman, 2009). In this work, mice from the same inbred strain were exposed to a band of noise placed in the region of best threshold sensitivity. The noise was titrated in level and duration to produce a large, acute threshold shift (30–40 dB at 24 h), but one that recovered by 2 weeks, without hair cell loss. Immunostained cochlear whole mounts and plastic-embedded sections (Fig. 1A–D), imaged by confocal and conventional light microscopy, were assessed to quantify hair cells, cochlear neurons, and synaptic structures providing the communication conduits. Hair cell-based distortion product otoacoustic emissions (DPOAEs) and neural-based auditory brainstem responses (ABRs) or compound action potentials (CAPs) of the auditory nerve were used to assess the peripheral consequences of the noise on function (Fig. 3A and B).

Presaging the ganglion cell losses, results of these studies revealed an acute loss of synapses between IHCs and the peripheral terminals of the spiral ganglion neurons that contact them (Kujawa and Liberman, 2009). Although thresholds recovered, by design, and no hair cells were lost, IHC synaptic losses were greater than 40% in basal cochlear regions, when assessed 24 h post noise, and were stable 2 and 8 weeks later. Losses were proportional in magnitude and cochlear location to the SGC loss observed in the previous series, suggesting that this interruption of IHC-to-neural communication set the stage for the neurodegeneration.

Subsequent studies showed that cochlear synaptopathy also precedes hair cell loss and threshold shift in the aging mouse ear (Sergeyenko et al., 2013). In the same normally aging inbred strain, IHC synapse counts decline steadily throughout life, with losses reaching ~50% in oldest ears and beginning well before significant loss of threshold sensitivity or outer hair cells (OHCs) (compare Fig. 1E and F). SGC losses follow, ultimately reaching about 40% although IHC losses are only ~5% in oldest ears. SGC losses also are closely parallel to those reported in an age-graded series of human temporal bones with preserved hair cells (Makary et al., 2011; see Fig. 6). Thus, the neural loss in these aging ears, as in the TTS ears, is primary rather than a secondary consequence of the loss of their IHC targets. Moreover, when animals received a single, TTS- and synaptopathy-producing exposure as young adults, ongoing synaptic and neural losses were larger than those that otherwise

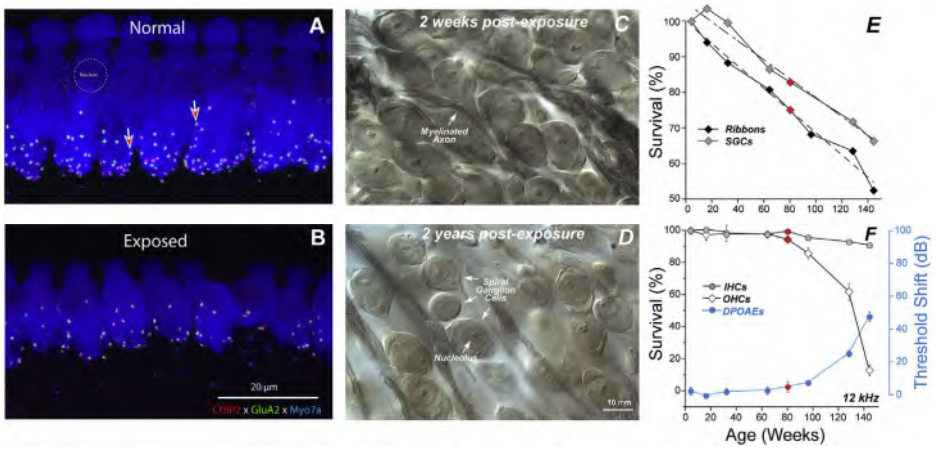

Fig. 1. Noise-induced and age-related loss of synapses and SGNs. Evaluating synaptopathy by triple-staining cochlear whole mounts for a pre-synaptic marker (CtBP2-red), a post-synaptic marker (GluA2-green) and a hair cell marker (Myosin VIIa-blue). Confocal z-stacks in the IHC area from a control **(A)** and a noise-exposed mouse **(B)**, 2 wks post exposure. Light micrographs of osmium-stained plastic sections from noise-exposed ears, 2 wks (**C**) or 2 yrs (**D**) post exposure. Exposure in **B** and **D** was 8–16 kHz, 2 h, 100 dB SPL, delivered at 16 wk to CBA/CaJ mice. **(E)** In aging ears from the same inbred strain, synaptic counts at IHCs decrease steadily from 4 to 144 wks and parallel ganglion cell loss follows whereas, **(F)** threshold loss begins comparatively later and accelerates beyond 80 wks, mirrored by accelerating loss of OHCs. IHC loss is trivial at any age. Red symbols flag 80 wk data points for all measurements. After Kujawa and Liberman 2006, 2009; Sergeyenko et al. (2013).

occurred in aging ears (Fernandez et al., 2015).

3. Glutamate excitotoxicity as an instigating factor

The IHC - cochlear nerve synapse is the primary conduit through which information about the acoustic environment is transmitted to the auditory nervous system. In the normal ear, 95% of cochlear nerve fibers make synaptic connection only with IHCs (Spoendlin, 1972). Each cochlear nerve fiber has a cell body in the spiral ganglion, a peripheral axon in the osseous spiral lamina (OSL) and an unmyelinated terminal dendrite in the organ of Corti, with a terminal bouton that forms a synapse with the IHC. The synapse is comprised of a presynaptic ribbon surrounded by a halo of neurotransmitter-containing vesicles within the IHC (Nouvian et al., 2006) and a postsynaptic active zone on the cochlear nerve terminal, with glutamate (AMPA-type) receptors for the released neurotransmitter (Puel, 1995; Glowatzki and Fuchs, 2002). Collectively, these synapses convey information about stimulus intensity and temporal properties over a wide dynamic range (Moser et al., 2006). As summarized in a recent review (Reijntjes and Pyott, 2016), the mechanisms supporting the diversity and breadth of afferent firing are likely resident within this complex, determining the intrinsic excitability of the neural elements, and the modulation of this excitability by chemical transmitters.

The time course of the initial events after exposure suggested a role for an excitotoxic process. Work by Puel and colleagues has shown that local application of glutamate receptor (GluR) agonists can produce dose-dependent swelling of cochlear nerve terminals contacting IHCs, as shown in Fig. 2. The dendritic swelling is observed under IHCs, but not OHCs, and is prevented by prior intracochlear perfusion of glutamate antagonists (see Ruel et al., 2007 for review).

There is similar longstanding evidence that cochlear neurons are directly targeted by noise, through excess sound-induced release of the endogenous neurotransmitter. Morphological studies have documented similar swelling of type I cochlear nerve terminals in the region of their synaptic contact with IHCs (Spoendlin, 1971; Robertson, 1983; Puel et al., 1998). Such terminal swelling can be

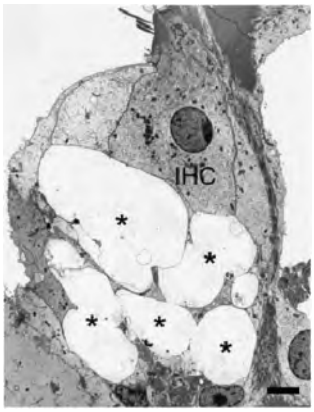

Fig. 2. Excitotoxic swelling in the cochlea. Infusion of AMPA (200 μM) in the cochlea triggers massive swelling of afferent endings (*) underneath the inner hair cell (IHC). Scale bar = 1 μM. From Ruel et al. (2007), with permission.

seen for exposures that produce PTS or TTS, including the exposure producing the neuropathy described here (8–16 kHz at 100 dB SPL for 2 h; Kujawa and Liberman, 2009). As for the glutamate agonist-induced excitotoxicity, the ultrastructural pathology in cochlear nerve terminals immediately after noise exposure is dramatic. Protection against the noise-induced swelling is provided by cochlear perfusion of the AMPA/kainate antagonist, kynurenate and by Riluzole, which may protect by inhibiting glutamate release (Ruel et al., 2005).

One working hypothesis (Kujawa and Liberman, 2009) is that this excitotoxicity is a primary initial event in the degenerative cascade observed after noise: 1) in the hours and days immediately post exposure, some unmyelinated terminal dendrites of SGCs degenerate back to the habenula as a direct effect of glutamate excitotoxicity, associated dendritic swelling and possible terminal rupture; 2) the loss of these peripheral terminals interrupts the

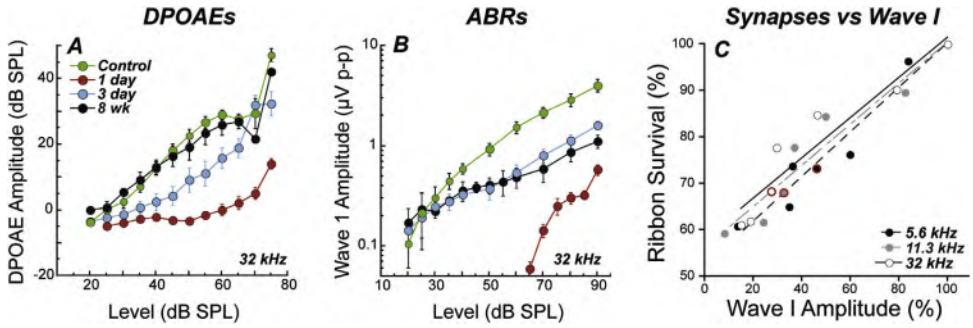

Fig. 3. Response amplitudes and synapse counts. Permanent reductions in ABR, but not DPOAE amplitudes in ears with recovered thresholds after noise. Shown are DPOAE (**A**) and ABR wave 1 (**B**) response growth functions in the region of maximum acute TTS 1 d and 2 wk after exposure (as in Fig. 1) to 16 wk CBA/CaJ mice; unexposed controls shown for comparison. Neural response amplitude declines are proportional to synaptic and neural losses in aging CBA/CaJ, where synapses are plotted vs mean wave 1 amplitudes (at 80 dB SPL in 4–128 wk animals **(C)**. Panels A,B from Fernandez et al., 2015; Panel C from Sergeyenko et al., 2013.

neurotrophin signaling required for normal development and maintenance of the cochlear innervation (Fritzsch et al., 2004; Ramekers et al., 2012; Stankovic et al., 2004) by removing the intimate association between cochlear supporting cells (or hair cells) and the neuronal Trk receptors for the neurotrophins; and 3) this interruption of neurotrophin signaling compromises the long-term viability of those neurons, essentially sealing their fate at an early stage of the process (though the subsequent intracellular balancing act between cell death and cell survival pathways may take months to resolve).

A key test of the hypothesized role of neurotrophins in the neurodegeneration that follows synaptic and terminal loss in these ears is provided by rescue experiments demonstrating synaptogenesis and recovery of function in a noise model (Wan et al., 2014; Suzuki et al., 2016). Given that loss of SGCs and their central projections is very slow after such insults, and IHC targets often survive, results suggest the exciting possibility of hair cell – neuron reconnection over a long therapeutic window in human application.

Although it is easy to imagine excess glutamate release resulting from prolonged, high-level acoustic stimulation, the glutamate excitotoxicity hypothesis must be reconciled with recent studies suggesting that IHC synaptopathy is also a primary effect of aminoglycoside antibiotics. As we have reported for noise exposure, others have shown that when aminoglycoside doses are titrated to levels below those causing hair cell loss, there can nevertheless be significant loss of synaptic terminals on IHCs (Ruan et al., 2014) and basal turn IHC synapses and SGCs (Oishi et al., 2015). Classic studies of aminoglycoside ototoxicity focused on the hair cells as primary targets and considered neural losses to be a secondary consequence of hair cell loss (McFadden et al., 2004; Takeno et al., 1998; Bae et al., 2008; Dodson and Mohuiddin, 2000). However, aminoglycoside-induced excitotoxic swelling of nerve terminals also has been reported in both cochlear and vestibular end organs (Basile et al., 1996; Duan et al., 2000; Sedo-Cabezon et al., 2014; Smith, 1999), suggesting direct, excitotoxic effects of these drugs on neural elements.

Recent studies also suggest that IHC synaptopathy may result from impulse noise exposure (Cho et al., 2013). Again, although it is easy to imagine high-level impulsive stimuli damaging by direct mechanical effects, it is not obvious why a stimulus lasting only microseconds should lead to over-release of neurotransmitter. Clearly, more research is necessary to understand whether all these elicitors of synaptopathy act via the same mechanism.

4. Functional effects of synaptopathy

The diffuse synaptic and neural loss observed in both noise-exposed and aging ears does not elevate thresholds. However, if DPOAE responses return to normal (after TTS-producing noise; Kujawa and Liberman, 2009, Fig. 3A) or have not yet deteriorated (in aging; Sergeyenko et al., 2013), the suprathreshold amplitude of ABR wave 1 (Fig. 3B) can be highly predictive of the degree of cochlear synaptopathy (Fig. 3C), as affected neurons are silenced with the loss of their synaptic connection to the IHC. Consistent with the innervation schema of a single auditory neuron communicating with a single IHC via a single synapse (Stamataki et al., 2006), and the basic idea that each fiber contributes a tiny current to ensemble far-field potentials (Antoli-Candela and Kiang, 1978; Buchwald and Huang, 1975), the fractional decrease in ABR wave 1 amplitude scales linearly with the fractional loss of synaptic connections in aging mice (Sergeyenko et al., 2013, Fig. 3C). And, demonstrating the specificity as well as the sensitivity of the wave 1 assay, such permanent neural response amplitude declines are not seen after noise exposures that fail to produce synapse loss (Fernandez et al., 2015). The robustness of the correlation in inbred mice, reviewed here, is likely enhanced by low inter-subject variability due to genetic homogeneity, as well as strict experimental control of intended and untended exposures. These variables will introduce challenges to the study of primary neurodegeneration in the human. Moreover, this correspondence is only straightforward if uncomplicated by hair cell damage, since disruption of mechanoelectric transduction also will reduce the ABR amplitudes.

5. Cochlear neurodegeneration and SR types: special vulnerability of low-SR neurons

In all studies completed thus far, neural loss has been subtotal, raising the possibility that cochlear insults are targeting a subpopulation of cochlear neurons. Auditory nerve fibers (ANFs) contacting IHCs differ in spontaneous rates (SR) of firing (low, medium, high), and their sound-driven firing rates vary over different ranges to support a large dynamic range of neural response (Liberman, 1978). Threshold sensitivity of ANFs is inversely correlated with SR; high-SR fibers have low thresholds, but saturate at levels where high threshold, low-SR fibers continue to code level with increasing firing rate (Winter et al., 1990). In addition to their higher pure-tone thresholds, low-SR ANFs tend to have larger dynamic ranges (Schalk and Sachs, 1980) and reduced susceptibility to excitatory masking by continuous noise stimuli (Costalupes et al., 1984). Thus,

although low-SR fibers are not needed for threshold detection, they are likely important for hearing in noise and for fine temporal precision at suprathreshold levels.

Two findings in work presented thus far suggested that the primary neural degeneration that inevitably follows noise-induced and age-related synapse loss might be biased toward the low-SR subgroup, which comprises roughly 40% of the ANF population (Liberman, 1978; Tsuji and Liberman, 1997). First, maximum neuronal loss is roughly 40–50% for a broad range of noise exposures (Kujawa et al., 2011) and in the unexposed, aged ear before hair cell loss is significant (Sergeyenko et al., 2013). Second, a selective loss of high-threshold fibers would provide a natural explanation for the full recovery of thresholds in ears with persistent suprathreshold neural amplitude declines after TTS. Subsequent studies have probed these relationships, as described below.

5.1. Single unit evidence for low-SR vulnerability

Neurophysiological studies suggest that neurons from the different SR classes are not equally represented in the noise-induced neuropathy (Furman et al., 2013). In these studies, recordings were obtained from single ANFs in guinea pigs after a noise exposure known to produce temporary threshold shifts with acute loss of synapses, as in the mouse model (Kujawa and Liberman, 2009). The proportion of fibers with low SR was significantly smaller in exposed than in control ears, particularly in cochlear frequency regions relevant to the exposure (Fig. 4A). Surviving high-SR fibers showed normal response properties, including normal thresholds and tuning (Fig. 4B), supporting the notion that OHCs were functionally normal and that low-SR neurons with high thresholds were selectively eliminated. Studies in gerbil provide two additional observations of the particular vulnerability of low SR neurons; to aging (Schmiedt et al., 1996) and to ouabain-induced neuropathy (Bourien et al., 2014). In the latter, the dose-response relation revealed first effects on low-SR neurons followed by medium- and then high-SR with increasing drug dose. The apparent vulnerability of low-SR neurons remains unexplained. Low- and high-SR neurons and their synapses distribute differently at IHCs; we speculate that different distributions of glutamate receptor subtypes may contribute to differences in the excitotoxic response to noise. Additionally, low-SR fibers are poor in mitochondria, which are important in buffering intracellular $Ca2+$; this characteristic might also increase their vulnerability to damage.

5.2. Morphology of synaptic vulnerability

Morphologic support for the preferential loss of low-SR neurons comes from studies in which 1) SR-related spatial distributions of ANFs at IHCs (Liberman, 1980, 1982), 2) presynaptic ribbons and postsynaptic glutamate receptor patches (Yin et al., 2014) and 3) post-noise reorganization of synaptic locations (Liberman et al., 2015) all suggest preferential vulnerability of low-SR neurons and their synapses after noise. Low- and high-SR fibers differ in synaptic position on the IHC and in the size of synaptic ribbons and associated AMPA-receptor patches (Liberman et al., 2011; Merchan-Perez and Liberman, 1996); low-threshold, high-SR fibers tend to synapse on the pillar side of the IHC, whereas the high-threshold, low-SR fibers tend to synapse on the modiolar side (Liberman, 1982). This physiological gradient also appears in confocal images from immunostained cochlear whole mounts as complementary gradients in ribbon and GluR-patch size on the pillar vs. modiolar sides of the IHC; large ribbons and small receptor patches tend to be localized to the IHC's modiolar side compared to small ribbons and large receptor patches on the pillar side (Yin et al., 2014). These gradients appear to be part of the morphological substrate for the low-SR/high-SR gradient in cochlear nerve response (Liberman, 1978).

In normal ears, the density of synapses tends to be greater on the modiolar side of the IHC (Fig. 5A). After noise, loss of synapses also appears greater on the modiolar side (Liberman et al., 2015), consistent with physiological reports of selective loss of low-SR fibers in this noise damage model (Furman et al., 2013). However, synaptic positions along the IHC's basolateral membrane appear to transiently redistribute along the habenular-cuticular and modiolar-pillar axes after noise, particularly within the region of greatest noise-induced synaptopathy, recovering by 1 wk post exposure. Thus, interpreting synaptic position after noise is complicated by dynamic changes that occur in the acute post-exposure time frame. Spatial segregation of high- and low-SR fibers in the OSL as shown in Fig. 5B and C may be useful in assessing which fiber type has degenerated after cochlear insult.

Other dynamic, post-noise changes to synaptic structure have been observed. In the normal cochlea, confocal images document

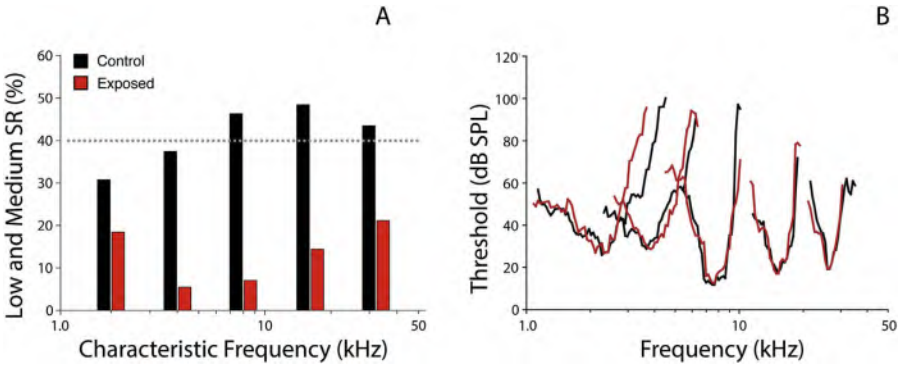

Fig. 4. Low-SR neuron loss after noise. Single unit recordings were made in guinea pigs 10 days after a TTS-producing noise exposure that resulted in permanent ABR amplitude declines and synapse loss but no hair cell loss. Spontaneous rate distributions suggest selective loss of low-SR fibers in the high-frequency region of maximum noise-induced injury **(A)**. In the same animals, thresholds and tuning of surviving nerve fibers, matched for CF, were not altered in noise exposed ears compared to controls **(B)**. The single-fiber database included 367 fibers from 14 control animals, and 382 fibers from 9 exposed animals. After Furman et al., 2013.

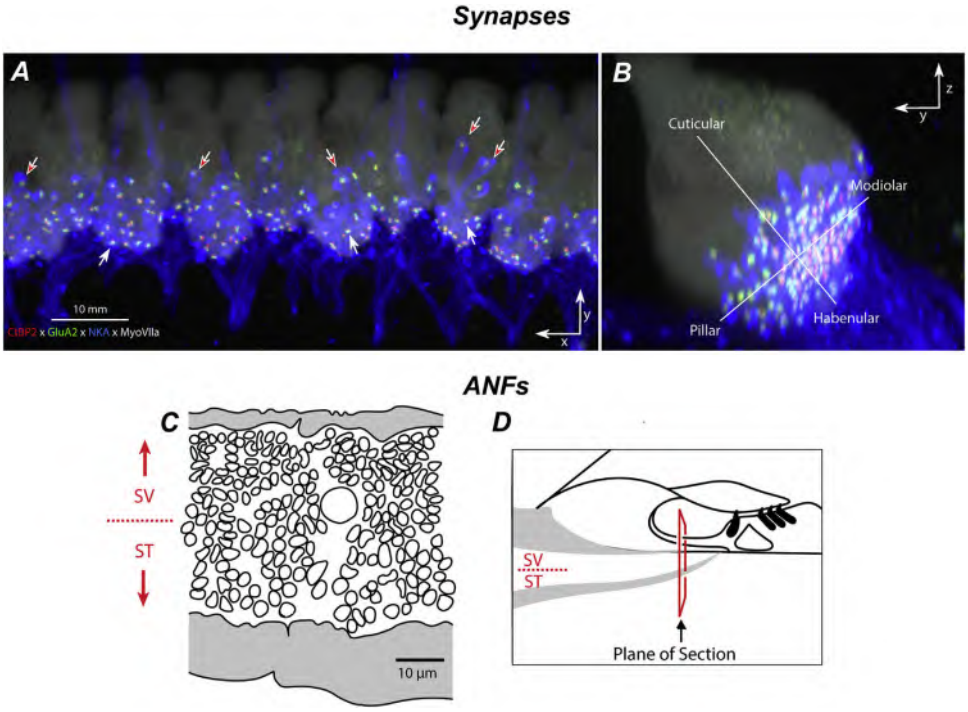

Fig. 5. Gradients in synaptic and afferent fiber morphology. IHC synapses in confocal z-stacks, acquired in the x-y plane **(A)** and re-projected into the y-z **(B)** plane. **A** Pre- and post-synaptic elements in the IHC area are counted in cochlear whole mounts quadruple-immunostained for CtBP2 (red), GluA2 (green), NaK ATPase (blue), and myosin VIIa (white). **B** Size gradients in pre- and post-synaptic elements are quantified according to location along habenular-cuticular and modiolar-pillar axes (Liberman et al., 2015). **(C)** Tracing of peripheral axons from a cross section through the osseous spiral lamina (OSL; **D)** in a normal cat shows the SR-based gradient from thin (low-SR) to thick (high-SR) fibers (Kawase and Liberman, 1992).

a one-to-one association between pre-synaptic ribbons and post-synaptic glutamate receptor patches (Kujawa and Liberman, 2009), consistent with ultrastructural analyses (Liberman, 1980; Stamataki et al., 2006). After noise, there is a transient increase in the number of 'orphan' ribbons, restricted to basal cochlear regions within the noise-damage focus (Fernandez et al., 2015; Liberman et al., 2015). This change in the number of GluA2 puncta could reflect a transient internalization of surface glutamate receptors, as documented previously in response to glutamate agonists *in vitro* or noise *in vivo* (Chen et al., 2007). This reversible down regulation of surface AMPA receptors may serve a protective function (Chen et al., 2007, 2009) by modulating synaptic strength.

Despite progress in describing morphological differences between low- and high-SR fibers and their contacts with the IHCs, mechanisms underlying the apparent vulnerability of low-SR neurons remain poorly understood. Neurotransmitter released from the IHC must be maintained at levels low enough to ensure high signal-to-noise ratio and to prevent excitotoxic damage to afferent neurons. Rapid clearance of synaptic glutamate is accomplished by the uptake system of glutamate transporters (Bridges and Esslinger, 2005; Danbolt, 2001; Hakuba et al., 2000; Seal and Amara, 1999) and immunostaining for glutamate transporters is less intense on the low-SR side of the IHC (Furness and Lawton, 2003). Low-SR fibers also have fewer mitochondria which, in the central nervous system, are well documented to be of fundamental importance to Ca^{++} buffering mechanisms and thus to the control of excitotoxicity (Szydlowska and Tymianski, 2010).

6. Cochlear synaptopathy and relevance to human SNHL

6.1. Synaptopathy in human temporal bones

Against this backdrop of animal studies, our working hypothesis is that partial de-afferentation of IHCs is widespread in human ears across a range of acquired SNHL etiologies, with or without overt hearing loss. Using immunostaining for pre- and post-synaptic elements as performed in the animal models, temporal bones from individuals 55–89 years of age with no explicit otopathology revealed dramatic cochlear synaptopathy, with afferent innervation density ranging from 15 synapses per IHC in a 55 yr old to only 2.5 synapses per IHC in an 89 yr old, despite no significant loss of IHCs or OHCs (Fig. 6B). As in normal-aging mice (Sergeyenko et al., 2013), SGC counts decrease throughout the lifespan and throughout the cochlea (Viana et al., 2015; Fig. 4B. In mice, the SGC counts underestimate the degree of IHC de-afferentation, because the SGCs survive for months after the loss of their peripheral synapses with IHCs. Similarly, observations in human temporal bones suggest that the loss of IHC synapses in normal-aging humans also can be significantly greater than the loss of SGCs (Fig. 6A). These data suggest that cochlear synaptopathy may be a major cause of functional impairment in age-related hearing loss in humans.

6.2. Synaptopathy, low-SR neuropathy and human auditory function

In summary, synapses are lost first as noise dose increases, and synapses are lost first as age progresses. This may be a general

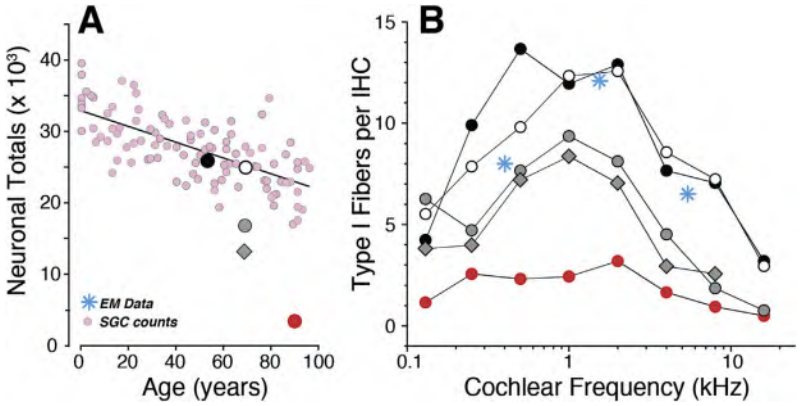

Fig. 6. Cochlear de-afferentation in human temporal bones. Cochlear de-afferentation is seen in human temporal bones as a function of age (**A**) and cochlear location (**B**) in cases with no hair cell loss and no explicit otologic disease. The small pink symbols **(A)** are estimated total SGC counts from archival sections (Makary et al., 2011); the five large symbols **(A)** are the estimated total peripheral axon counts from the same five cases shown in **B**. Counts of cochlear nerve terminals per IHC **(B)** in 5 normal aging temporal bones (55–89 yrs) with no history of otologic disease (Viana et al., 2015). Blue symbols are counts of synapses per IHC from an electron microscopic study of a normal middle-aged human (Nadol, 1988).

finding in other forms of acquired SNHL common in humans, as well. Affected neurons are silenced by the loss of this synaptic connection, even if it takes months to years for the loss to be reflected in SGC loss. Audiometric thresholds are unaffected by diffuse synaptopathy; however, such dramatic disconnection of hair cells and ANFs must have significant perceptual consequences.

Normal response properties of low-SR neurons, in quiet and in noise, have led to speculation regarding functional consequences of their targeted loss. Low-SR neuropathy may be a major contributor to a classic impairment in SNHL, speech-in-noise difficulty (see Kujawa and Liberman, 2015; Plack et al., 2014 for discussion). This notion is not new; low-SR neuropathy has been suggested to contribute to well-documented performance declines with age that include decreased speech understanding in noise and reduced ability to utilize stimulus timing and amplitude modulation cues (Schmiedt et al., 1996). It also may be important in limiting psychophysical performance in "normal hearing" human listeners; that is, those with good threshold sensitivity, and it may help account for performance differences in individuals with similar, elevated audiometric thresholds. In support, deficits in binaural temporal processing, seen as a decrease in the detectability of interaural phase differences in amplitude modulated tones, are highly correlated with changes in ABR responses consistent with the selective loss of low-SR fibers (Bharadwaj et al., 2014, 2015).

Cochlear synaptopathy also may be a key elicitor of what are commonly the most troubling sensory anomalies associated with SNHL, tinnitus and hyperacusis. This may be the result of a compensatory plasticity, wherein the synaptic gain in auditory central circuits is increased when neural signals from the periphery are attenuated (Bauer et al., 2007; Gu et al., 2010; Hickox and Liberman, 2014; Kaltenbach and Afman, 2000; Knipper et al., 2013; Roberts et al., 2010; Schaette and McAlpine, 2011). Results support the long-standing hypothesis that reduced afferent outflow from a damaged cochlea and the associated diminished input to higher auditory centers drives increases in central gain that may, in turn, underlie tinnitus.

Work in this area is in its infancy, and ultimately will be crucial to the translation of these findings to humans, where the histopathology will not be available in life. The TTS animal model of primary neuropathy has provided a powerful platform to characterize synaptopathic/neurodegenerative consequences of noise exposure and to begin to test hypotheses about the special role(s) of low-SR fibers in auditory processing without the confounding variables of hair cell damage and threshold shift. The recording of thresholds and suprathreshold amplitudes of OHC-based DPOAEs and neural-based ABRs in the same ears provides a valuable window into the underlying histopathology in ears with normal thresholds; ABR wave 1 amplitudes recorded in such ears scale closely with the underlying synaptopathy. However, acquired SNHL in humans will encompass a range of threshold losses and underlying damage that may include mixed loss of hair cells and synaptic contacts on surviving IHCs. Metrics robust to such mixed involvements and accompanying threshold elevations will be required. Experiments underway have undertaken assessment of synaptic and functional losses for a range of TTS- and PTS-producing exposures, with and without hair cell loss.

6.3. *Monitoring for synaptic injury and treatment efficacy*

Pure tone threshold audiometry serves as the standard metric for assaying the effects of noise, ototoxic drugs and other agents on hearing in clinical and occupational settings. Threshold measurement protocols have undergone extensive vetting and standardization. Such measurements also form the basis for population sensitivity norms to which individual sensitivity is compared, and threshold-based estimates of noise risk have informed recommended and enforced occupational exposure standards (e.g. NIOSH, 1998; OSHA, 1983).

Against this backdrop, the standard of care in clinical and occupational monitoring for hearing damage in noise- and ototoxic drug-induced injury is assessment of exposure-related changes in threshold sensitivity (OSHA, 1983; ASHA, 1994; AAA, 2009; ACOEM et al., 2012). Such a strategy, particularly if it includes extended high-frequency threshold and OAE monitoring, should be valuable as an early warning of hair cell injury and loss as well as impending performance declines due to reduced audibility. If synapse loss in humans precedes threshold elevation and OHC loss after noise or ototoxic drugs, as it does in all animal models evaluated thus far, clinical decision making and occupational health monitoring protocols would require revision to identify earliest injury, with the goal of preserving hearing function. Similarly, should treatments aimed at preserving, protecting or regenerating cochlear synaptic connections materialize, assays of function with sensitivity to the functional integrity of the synaptic machinery will be required.

Preliminary studies in humans have suggested several non-invasive assays that may provide important clues to underlying synaptopathy (Liberman et al., 2016; Mehraei et al., 2016), as has been shown directly in the animal models of noise and aging reviewed here.

7. Summary

New insights from animal studies of noise-induced and age-related hearing loss suggest that the most vulnerable elements in the inner ear are the synaptic connections between hair cells and sensory neurons. Subtotal cochlear synaptopathy, and the primary neural degeneration that follows, does not elevate thresholds. Thus, it can be widespread in ears with intact hair cell populations and normal audiograms. It also occurs in ears with sensory cell injury and loss, resulting in a mixed sensory-neural pathology. We hypothesize that de-afferentation of surviving IHCs may be a major contributor to auditory dysfunction in numerous etiologies of acquired SNHL. Thus, the result has profound human health ramifications. These discoveries are recent, and much remains to be clarified. In our laboratories, the synaptopathy has been largely permanent, indeed progressive, in multiple species. There are reports, however, that spontaneous re-innervation can be seen (Puel et al., 1995; Pujol and Puel, 1999; Sun et al., 2001), or that some of the immediate synapse loss may be reversible (Liu et al., 2012; Shi et al., 2013, 2015; 2016; Song et al., 2016). The source(s) of these discrepancies remain to be identified. Work is ongoing to study the phenomenon, to probe its mechanisms, and to assess the efficacy of a possible therapeutic intervention, using cochlear insults that are highly relevant to the human condition.

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Discussion Paper on Hearing Loss

Prepared for the Veterans Review and Appeal Board

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Abnormalities in vestibular end organ function often result in the patient experiencing the subjective complaint of vertigo.

d. Physiology of Hearing

Sound vibrations are picked up by the pinna and transmitted down the external auditory canal where they strike the TM causing it to vibrate. The sound vibrations are then transmitted across the air-filled middle ear space by the 3 tiny linked bones of the ossciular chain: the malleus, incus and stapes. The mechanical vibrations are transmitted to the inner ear via the vibrations of the stapes footplate.

When the mechanical vibrations of the stapes footplate reach the inner ear they create traveling waves in the cochlea. The hair cells change these mechanical vibrations from the waves into electrochemical impulses that can be interpreted by the central nervous system (CNS). The tiny cilia (little hairs) on top of the hair cells (both inner and outer) are covered by a gelatinous membrane called the tectorial membrane. Fluid waves in the inner ear cause a deflection of both the tectorial and basilar membranes that surround the organ of Corti. The cilia move and generate a nerve impulse called a generation potential (GP). When enough generation potentials occur they result in what is called an action potential (AP). The transmission of electrical activity along the cochlear nerve will ultimately make its way through a series of nuclear relay stations within the brainstem (this concept forms the basis of the electrophysiological test called the *auditory brainstem response* or *ABR*). Electrical signals are then forwarded to the auditory cortex in the temporal lobe for decoding. How we perceive what certain electrical signals represent in our auditory cortex forms the basis for the field of *psychoacoustics* (i.e. the perception of sound).

Although the vast majority of the cochlear nerve fibres are termed *afferent* (i.e. nerves that carry electrical activity from the inner ear to the brain), within the cochlear nerve itself we have a small number of nerve fibres designated as *efferent* (nerves that carry electrical activity from the brain to the inner ear). Most of the efferent fibres seem to land on the outer hair cells of the organ of Corti. This apparent internal "feedback loop" is thought to be responsible for "fine tuning" hair cell responses by inhibiting some unwanted electrical impulses and by changing the mechanical properties of the basilar and tectorial membranes. The presence of active non-muscular contractile elements within the outer hair cells and their effects on movement of the basilar membrane is used to explain the concept of *otoacoustic emissions* (OAEs) testing.

Of interest when the outer hair cells become injured or are affected by pathology is they also lose their ability to "fine tune" the electrical responses arising from the inner ear. The phenomenon of *recruitment* represents an abnormal sense of loudness. Distortion of certain sounds arises when enough hair cells are damaged such that the hearing threshold is reduced. When the sound gets loud enough, the inability to "fine tune" sound becomes lost and more nearby hair cells are drawn into the firing needed to create an electrical signal; hence the distortion of a loud sound.

Although an individual may have apparently normal hearing it does not necessarily mean the cochlear nerve is undamaged. It is estimated that up to 75% of the auditory nerve supplying a certain section of the cochlea can be injured without causing an appreciable change in pure tone threshold hearing. This may be one reason why certain individuals with tumors arising on the nerves of balance and hearing, better known as *acoustic neuromas* (vestibular schwannomas), often preserve their tonal perception of sound yet have problems with its discrimination (i.e. they know someone is talking on the telephone but can't understand what is being said in the affected ear).

e. Some Physical Considerations of Sound

Sound is the propagation of pressure waves through a medium such as air and water for example. It can be a simple sound commonly known as a pure tone or it may be complex when we think of speech, music and noise. A cycle of a pure tone is represented by a sine wave appearance with an area of compression followed by rarefaction.

Pure tones have several important characteristics. Frequency represents the number of cycles per second or Hertz (Hz). Low sounds tend to have a long wavelength relative to higher pitched sounds which have shorter wavelengths by comparison. The physiologic correlate of frequency is pitch. In general terms the greater the frequency the higher the pitch of the sound, and the greater the intensity the louder we hear it. The degree of intensity or loudness of a sound is measured in decibels (dB). In complex sounds the interaction of its pure tone components forms the basis of its complexity or its psychological counterpart known as timbre.

The decibel (dB) is an accepted measure of sound pressure level used to describe sound intensity. It is based on 1 Bel (B) being equal to an accepted sound pressure level of 0.0002 dynes/cm^2 (20 uN/m^2 or 20uPa). The concept of the decibel is based on the pressure of one sound or reference level with which the pressure of another sound is compared.

Because of the large numbers involved for sound pressure measurement, dB scales have been created for convenience (i.e. 100 Bel =10^2 Bel = 0.02 dynes/cm^2 =$2_{(\log 10)}$ Bel or 20 dB; 10,000,000 Bel = 70dB). The greater the dB reading at any frequency, the worse an individual's hearing is. Because the dB scale is presented in a logarithmic fashion on the audiogram, it is important to note that the difference between sound pressure levels of 30 to 60 dB is not 30 but represents noise levels that are 10^3 or 1000 X's greater in intensity.

3. Overview of Hearing Loss

a. Types of Hearing Loss

Hearing loss in any individual at any given time is a combination of the following factors:

a. Congenital (what were they born with)
b. Acquired (what they developed as a result of pathological exposures or processes during their lifetime)

The entities of nosiocusis (hearing loss from pathologic processes), sociocusis (from everyday noise exposure) and presbycusis (from age related change) form the subgroups of acquired hearing loss.

Conceptually three types of hearing loss exist:

1. Sensorineural
2. Conductive
3. Mixed (a combination of sensorineural and conductive hearing loss)

A sensorineural hearing loss exists with injury to the cochlea or the cochlear nerve. This is the type of hearing loss that is found in routine, unprotected daily exposure to loud noise potentially injurious to hearing in the occupational work force or from recreational exposure.

A conductive hearing loss occurs when there is some interference of sound transmission or vibration due to pathology involving the external and/or middle ear. This type of loss might be found in an individual for example with a large tympanic membrane (TM) perforation where mechanical vibrations along the ossicular chain are dampened.

A mixed hearing loss occurs when both a sensorineural and conductive hearing loss are present at the same time. For example, an individual with a large TM perforation who received topical antibiotic ear drops for the treatment of a middle ear infection that caused inadvertent toxicity to the inner ear in addition (i.e. topical ototoxicity).

CONDUCTIVE HEARING LOSS	SENSORINEURAL HEARING LOSS
1. External otitis (acute and chronic)	1. Occupational or Noise Induced Hearing Loss (NIHL)
2. Wax	2. Presbycusis
3. Exostoses/osteomas	3. Menière's Disease
4. Acute Otitis Media	4. Ototoxicity (Systemic and Topical)
5. Otitis Media with Effusion	5. Cochlear Otosclerosis
6. TM perforations	6. Trauma
7. Chronic Suppurative Otitis Media (CSOM) a. Safe or mucosal CSOM b. Cholesteatoma	7. Acoustic neuromas (vestibular schwannomas)
8. Otosclerosis	8. Sudden Sensorineural Loss

b. Common Causes for a Sensorineural Hearing Loss

i. Noise induced Hearing Loss

According to the 1990 Noise and Hearing Loss Consensus Conference, "Noise Induced Hearing Loss (NIHL) results from damage to the ear from sounds of sufficient intensity and duration that a temporary or permanent sensorineural hearing loss is produced. The hearing loss may range from mild to profound, may result in tinnitus (unwanted head noise) and is cumulative over a lifetime." *Occupational* NIHL and *presbycusis* (degenerative hearing from aging change) represent the two most common causes of sensorineural hearing loss in society today.

Two types of noise exposure are associated with NIHL: *transient* and *continuous*.

Impact (i.e. the collision of two solid objects as might occur in a forge plant) or *impulse* (i.e. the sudden noise of an explosion) noise are examples of transient noise where there is a rapid rise in sound pressure and very quick decline over 0.2 seconds. Constant (*continuous*) or steady state noise by comparison remains relatively constant and lasts longer although fluctuations in sound intensity may occur. Although short lived, most impact/impulse noise typically has peak intensity levels much higher than found in steady state noise exposure. All things being equal, most noise in industry is a combination of continuous and superimposed impact noise.

When susceptible, unprotected ears are exposed to loud noise potentially injurious to hearing , the inner ear seems to react in one of three ways: by adapting to the noise (i.e. the inner ear seems to "toughen" in some individuals), by developing a *transient threshold shift* (TTS) or a *permanent threshold shift* (PTS).

TTS refers to a transient sensorineural hearing loss lasting hours to a few days. Hearing thresholds are depressed until the metabolic activity in the cochlea recovers. For this reason, workers ideally should be out of noise for at least 24 if not 48 hrs prior to audiometric testing to avoid the effects of TTS on hearing.

PTS refers to a permanent loss of sensorineural hearing which is the direct result of irreparable injury to the organ of Corti. Noise induced deafness generally affects hearing between 3000-6000 Hz with maximal injury centering around 4000 Hz initially, an important point to remember.

in presbycusis are typically non-specific and can also be seen in a vast number of pathologies including the effects of noise upon the inner ear.

Clinically, hearing loss from presbycusis appears to be an accelerating process unlike hearing loss in NIHL. In this regard, *the effects of aging in the absence of other factors cause a loss of hearing at all frequencies whose rate of growth becomes more rapid as age increases (especially after 60 years*): an important point to remember in this context.

Unfortunately, there is no specific treatment available that will prevent age related hearing loss at present. To a large degree hearing loss with age is genetically primed; in other words, the hearing your parents had as they aged is often passed on to you – usually, but not always.

a. Controversies between presbycusis and NIHL

In the adjudication process of an occupational NIHL claim, it is often difficult to separate the total amount of hearing loss from noise and age-related change.

For example, not everyone as they age will experience age-related presbycutic change (changes from presbycusis are variable with some individuals experiencing greater degrees of age-related change than others).

Moreover, exposure to high level noise early on may produce hearing loss more rapidly than aging, such that the aging process has a negligible effect (i.e. the more that has been lost early on, the less there is to lose later on) and so on and so forth.

b. Dobie's and Corso's Theorems

The effects of noise exposure and aging on hearing when not combined are reasonably well understood. When the two processes are combined, the resultant pathology and their effects upon hearing are not as well understood.

Although it seems logical to "subtract" the age-related effects from the total hearing loss in order to quantify the amount of hearing loss due to noise, this is really quite simplistic when one considers that aging effects and noise exposure can at times be practically indistinguishable from one another.

Because compensation claims have required some consideration of presbycusis and its role in the total hearing loss of an individual, various correction factors have been applied.

Dobie's theorem states that the total hearing loss from noise and age are essentially additive (this is the theory put into practice when a standard correction factor after age 60 years is applied, in the Province of Ontario for example).

Corso's theorem on the other hand states that any correction for age should be based on a variable ratio (as individuals age, the assumption is that the effects of presbycusis variably accelerate by decade). This certainly generates a more complicated mathematical model but probably more closely approaches what is happening physiologically.

Nevertheless, quantification of hearing loss attributable to age when occupational NIHL is present is really quite a complex phenomenon.

3. Does previous noise exposure make an ear more sensitive to future noise exposure?

Apparently it does not. It is generally thought that if an ear has suffered a permanent threshold shift from a noise induced etiology, then further noise exposure will cause less damage than would occur in a normal ear to a similar exposure. This is based primarily on animal modes which have demonstrated that at the frequency range of maximum damage, the increase in a noise induced PTS from the second exposure was smaller for ears with greater pre-existing loss (the so-called "you can't further damage what has already been damaged" rule).

The following example illustrates this rule:

Person A and Person B were both exposed to a similar event.

Person A had a pre-existing PTS to 20 dB.
Person B had no previous noise exposure and had no PTS.

Following similar noise exposure at the same instance,

Person A displayed a TTS to 45 dB - a loss of 25 dB.
Person B (who had no dB loss due to noise exposure) displayed a TTS to 45 dB - a loss of 45dB.

Person A's loss was 20 dB while Person B's loss was 45dB.
Person B's previously unaffected hearing received the most damage.

To conclude, this is really defined by what is called Corso's theorem, which implies that the majority of noise induced hearing loss occurs early on in noise exposure. Once the hearing loss has occurred one would not anticipate further injury to what has already been lost. Continued exposure, however, would be expected to continue to worsen hearing (albeit at a slower rate) and for that reason the use of hearing protection would still be recommended.

4. Does previous NIHL accelerate the onset of presbycusis?

This is question that continues to intrigue auditory research scientists. As previously noted, the effects of noise exposure and aging on hearing when <u>not</u> combined are reasonably well understood. When the two processes <u>are</u> combined, the resultant pathology and its effects upon aging are not as well understood.

It is likely that the two effects are not additive (Corso's theorem) but from a practical point of view this is how they are usually viewed with regards to compensation claims (Dobie's theorem).

Some generally accepted principles (according to the American Academy of Otolaryngology (AAO) - Head and Neck Surgery 1994 Guidelines) with regards to age-related change note that:

a. At any given age for frequencies above 1000 Hz men will have more age-related hearing loss than women.
b. Age-related hearing loss affects all frequencies, although the higher frequencies are usually more affected.
c. Age-related hearing loss is an accelerating process where the rate of change increases with age.

5. Does permanent damage to the cochlear hair cells caused by noise exposure contribute to the eventual development of a hearing disability?

There is a significant redundancy within the inner ear as it pertains to hearing. In other words, many hair cells in a similar region of the cochlea will encode for certain frequency response to sound stimulation. Hair cell loss can continue until a certain critical point is breeched with the individual unaware of any hearing deficit. Once the critical loss of hair cells occurs, however, the individual will notice a hearing loss.

One can speculate that this might be one of the reasons an individual early on in their exposures may not be aware of a hearing loss, only to appreciate a hearing loss later in life when other factors such as presbycutic change occur.

The issue can be debated but at present we have no means of actually knowing on clinical grounds the degree of hair cell damage that has occurred on a microscopic basis from noise exposure in a living individual if hearing is still deemed as normal. As previously mentioned there is a certain redundancy of cochlear hair cells for tonal awareness and one can probably have significant loss of hair cells yet maintain normal hearing. Once noise exposure has stopped other factor(s) would need to be involved to therefore worsen hearing. Nevertheless the cochlear hair cells reserve is probably not as great as it once was. That usually is the reason why we state that following noise exposure other factor(s) would be likely to cause further hearing loss in an individual.

6. *At what age does presbycusis begin to make a material difference to hearing disability and at what age can its effects be seen on an audiogram?*

When we are born we can hear frequencies up to 20,000 Hz. Over the years we hear less and less. Because we tend to make little use of frequencies > 8000 Hz we do not become aware of a hearing loss in general until the frequencies < 8000 Hz are affected.

Although we think of presbycusis as an age-related event, not all individuals will develop this condition. Moreover, we really don't have a lot of good prospective long-term studies over 4-5 decades that can ultimately answer this question completely. Upon saying this, however, we can actually demonstrate that many individuals will start to show early changes in hearing as early as age 40 years (in subjects screened to rule out other ear disease and noise exposure).

With regards to the rate of hearing loss noted in presbycusis, recent evidence from longitudinal prospective studies from Denmark and the UK indicate that the actual rate of deterioration seems to be influenced by age; those over 55 years showed a higher rate of deterioration of up to 9 dB/decade against a deterioration of 3 dB/decade for those under 55 years.

Future genetic studies may provide us with further information concerning those at greater risk for progressive hearing loss from presbycusis in future.

7. *Can moderate workplace noise exposure causing a TTS and repeated exposures later cause a PTS?*

Yes, repeated noise exposure that causes a temporary threshold shift (TTS) can ultimately lead to a permanent threshold shift (PTS) with repeated exposures. It is agreed that hearing loss and injury to the ear increases with the noise level, the duration of exposure, the number of exposures and the susceptibility of the individual.

A TTS is considered to represent a pathological metabolically induced fatigue of the hair cells or other structures within the Organ of Corti. Its development and recovery are proportional to the logarithm of exposure time. It reverses slowly over a period of hours. The practical "cutoff point" for a TTS is approximately 40dB. Below this threshold, recovery time is relatively swift; above this threshold, it appears delayed. If a person experiences repeated TTS with a shift in excess of 40 dB, the recovery time is longer and can result, over time, in a PTS.

In a PTS the destruction and eventual cochlear hair cell loss is thought to arise from direct mechanical destruction from high-intensity sound and from metabolic decompensation with subsequent degeneration of sensory elements.

While one would normally expect full recovery of hearing function after a TTS, there is one important consideration that needs to be taken into account. Some of this is based on the redundancy principle within the inner ear: *not all hair cells possibly recover following a TTS but enough do so as to prevent hearing loss.* Continued exposure to excessive noise will therefore result in further hearing loss.

In other words, when an ear sustains a TTS, it is conceivable that there may be some permanent injury to some of the inner/outer hair cells at the frequencies tested that is not reversible. Thankfully there is a significant amount of redundancy in the inner ear. It is only when a quantum number of hair cells are injured irreparably that we then begin to clinically notice a permanent threshold shift (PTS) in hearing.

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Noise and sound: Hearing loss and tinnitus

On this page

- Warning signs of hearing loss

Hearing loss

The primary causes of permanent hearing loss are age and exposure to loud sounds.

Age-related hearing loss:

- is permanent
- happens slowly
- affects both ears
- **can't** be avoided
- can't be cured, only managed
- can range from mild to severe
- is a common problem linked to aging
- typically begins later in life and isn't usually detected until after the age of 50

Anyone can experience age-related hearing loss as they get older. However, it can happen much earlier for people who don't take proper care of their hearing while:

- working in noisy places
- participating in noisy activities

When hearing loss is caused by exposure to loud sounds, it is called noise-induced or sound-induced hearing loss.

Sound-induced hearing loss:

- **can** be avoided
- can start at any age
- affects 1 or both ears
- can range from mild to severe

- can't be cured, only managed
- usually happens slowly, but it can be sudden if the sound is loud enough
- can be temporary at first, but become permanent with repeated loud sound exposure
- is a common problem for people who are frequently exposed to loud sounds and who don't take steps to protect their hearing

Both age-related and sound-induced hearing loss are types of sensorineural hearing loss. People with these types of sensorineural hearing loss will have similar difficulties in their daily lives depending on the severity of the hearing loss.

Mild hearing loss can make communication difficult. People with mild hearing loss may miss certain parts of conversations, especially over the phone. Mild hearing loss can make it difficult to:

- understand higher pitched voices
- properly hear consonants like "f," "t" and "s"
- tell the difference between the "sh" and "th" sound in speech

These difficulties can:

- have a negative impact on relationships
- lead to miscommunication and frustration

Most people who have mild hearing loss aren't even aware they have it. In a study that looked at hearing loss among people in Canada between the ages of 40 and 79, 8% of men and 5% of women self-reported hearing impairment. But when researchers measured the hearing of participants in the study, they found that 63% of men and 46% of women had measurable hearing loss.

Mild hearing loss can get worse over time and become moderate, especially with repeated exposure to loud sounds. Someone with moderate hearing loss will often need to ask people to repeat themselves or to speak louder when communicating in person and on the phone. If someone's hearing loss becomes severe enough, they won't be able to follow conversations unless they have hearing aids.

Difficulty communicating can impact relationships leading to smaller social networks and feelings of loneliness. In children and adolescents, even minimal hearing loss can have effects on:

- academic performance
- language development
- social and emotional development

In adults, hearing loss and impairment is associated with:

- anxiety
- depression
- low income
- decreased employment opportunities

Tinnitus

Exposure to loud sounds can cause tinnitus, a symptom of damage to the hair cells in the inner ear. Tinnitus is often referred to as a phantom ringing in 1 or both ears, however some people experience it as hissing, ringing, roaring, clicking, buzzing or other sounds.

Tinnitus can be temporary or permanent. For some people, experiencing temporary tinnitus doesn't bother or annoy them. For others, it's been associated with:

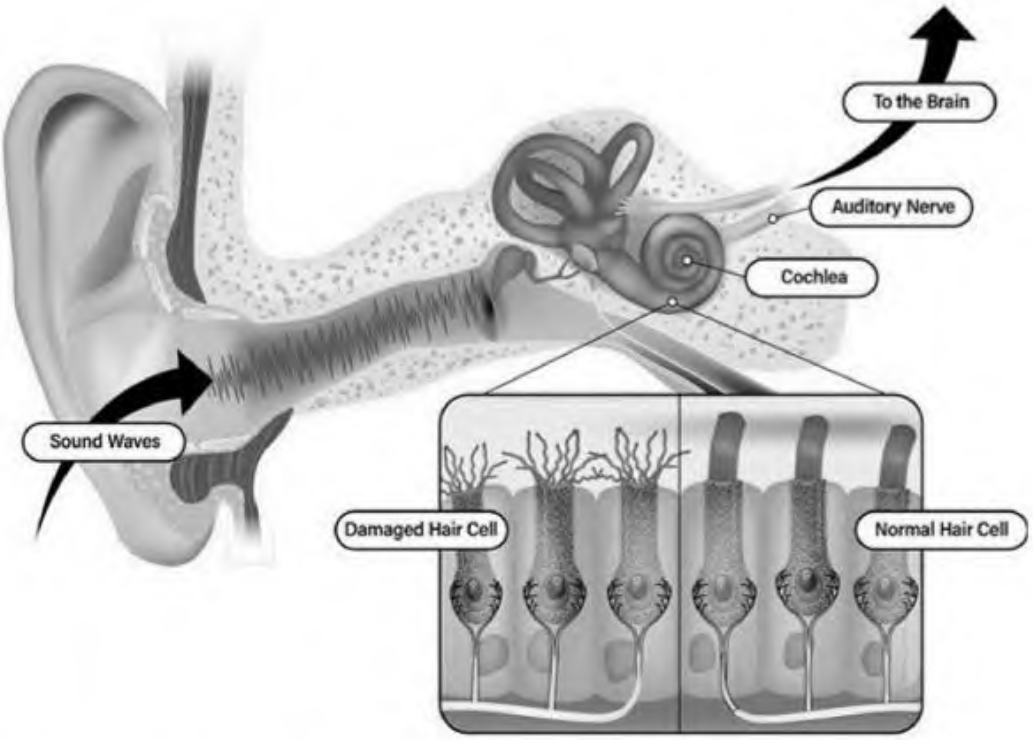
- stress

- anxiety
- irritation
- insomnia
- depression
- social isolation
- sleep problems
- feelings of loneliness
- difficulty concentrating

Tinnitus can occur because of exposure to loud sounds, such as attending a concert without hearing protection. Tinnitus can happen without hearing loss but it might also be a sign of hearing loss that's imminent or already present. Like hearing loss, there's no known cure, only treatments to help manage the symptoms.

Health reports: Tinnitus in Canada

How loud sound affects your ears over time



When sound reaches your ears, it travels along your ear canal to your eardrum causing it to vibrate. The vibrations are transmitted by 3 small inner ear bones into your inner ear (cochlea). In the cochlea, there is fluid and hair cells, also known as sensory cells. These hair cells convert sound into electrical signals that travel along the auditory nerve to the brain. Your brain interprets the signals as things like speech, music or noise. You're born with a set number of hair cells. Once they die, your body doesn't replace them.

Loud sounds damage the hair cells in your cochlea. Hair cells are rigid structures and regular exposure to loud sound causes them to lose their rigidity over time. Like grass that's stepped on, hair cells get bent by sounds. This is especially true for loud sounds.

Grass eventually dies when it's repeatedly walked over or trampled. Similarly, hair cells can be 'trampled' by loud sounds until they die and can no longer convert sound into electrical signals for the brain. This happens faster:

- the longer your ears are exposed to loud sounds
- the louder the sound with fewer breaks in between the exposure

These physical changes to the ear present as tinnitus, hearing loss or both. Sometimes, this can also present as hyperacusis, a disorder where a person becomes even more sensitive to sound because of damage to the hair cells.

Have you ever experienced temporary hearing loss or tinnitus after a loud sound exposure, like being at a concert or sporting event? If so, it means there was permanent damage done to some of your thousands of hair cells. They may have died off or become very broken. That damage will add up to permanent problems over time.

The likelihood that you'll develop hearing loss, tinnitus or both depends on:

- how loud the sound is
- how long you're exposed to it
- how often you repeat that pattern

For example, you are more likely to develop hearing loss, tinnitus or both if you:

- attend loud parties, dance clubs or other live music or sporting events without hearing protection weekly **and**
- listen to loud music or other audio using headphones daily **and**
- work in a noisy environment without hearing protection **and**
- do this over several years

The effect that loud sounds have on your hearing is cumulative. Repeated exposure to loud sounds and noise in earlier years could speed up age-related hearing loss in later life, more than what would be expected due to the natural process of aging.

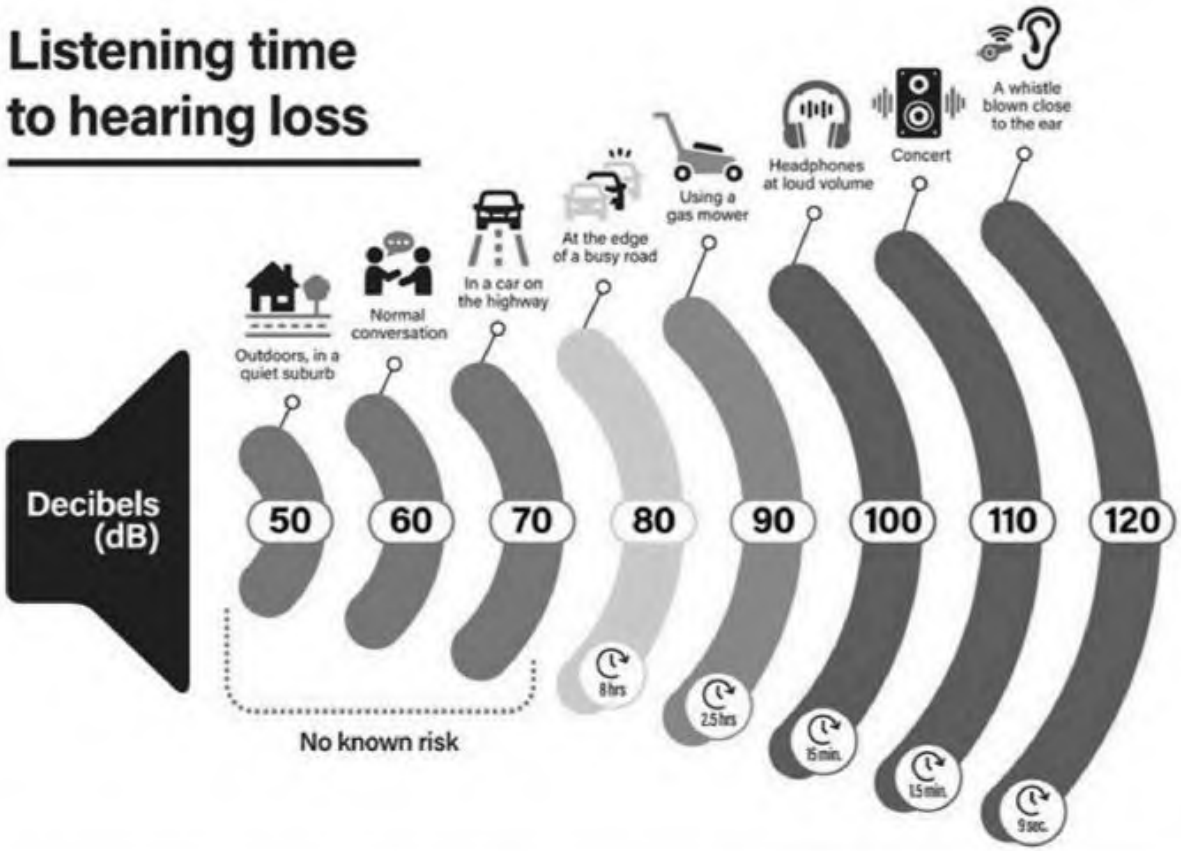
How to tell if a sound is too loud

Sounds with levels below 70 dBA pose no known risk of hearing loss, no matter how long the exposure lasts. A sound level of 70 dBA is about what you would experience while driving alone in a car at highway speeds with the windows closed and the radio off.

For sounds at levels higher than 70 dBA, the amount of time you're exposed becomes an important factor. For example, listening to music:

- at 85 dBA for 45 minutes a day poses no known risk of hearing loss
- at 85 dBA or higher for 8 hours a day can pose a significant risk of hearing loss

85 dBA is about what you would experience standing on the corner of a busy city street with lots of traffic going by.



▶ Listening time to hearing loss - Text description

Warning signs of hearing loss

Know the warning signs of early hearing loss and talk to a healthcare professional if:

- you think that people are mumbling
- you have a feeling of fullness in your ear
- you need to turn the volume on the tv or radio up more than you did in the past
- someone in your household consistently complains you have the volume turned up too loud
- someone you know well and see often tells you they think you need to have your hearing checked

- you hear a hissing, ringing, roaring, clicking or buzzing sound in your ear when there's nothing making these sounds
- you have difficulty trying to follow a face-to-face conversation with someone in a location where there's a lot of background noise, like at a restaurant
- you have difficulty trying to follow a conversation while talking on the phone while there are background sounds, for example, the TV is on or you're in a busy cafeteria

Check your hearing: Download the HearWHO App

Date modified:
2024-05-29

MSD MERCK MANUAL
Professional Version

Hearing Loss

*By **Mickie Hamiter**, MD, New York Presbyterian Columbia*

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Worldwide, about half a billion people (almost 8% of the world's population) have hearing loss (1). Approximately 15% of American adults (37.5 million) ages 18 and over report some trouble hearing. About 2 to 3 out of every 1,000 children in the United States are born with a detectable level of hearing loss in one or both ears (2). During childhood and adolescence, the prevalence of moderate to severe hearing loss increases to 6 out of 1,000 (3). Adolescents are at risk from excessive exposure to noise, head trauma, or both. Older adults typically experience a progressive decrease in hearing (presbycusis), which is directly related to a combination of aging, noise exposure, and genetic factors. Approximately 5% of adults ages 45 to 54 have disabling hearing loss. The rate increases to 10% for adults ages 55 to 64 years. Approximately 22% of those ages 65 to 74 and 55% of those who are 75 years and older have disabling hearing loss (2). It is estimated that about 30 million people in the United States are exposed to injurious levels of noise on a daily basis.

Hearing deficits in early childhood can result in lifelong impairments in receptive and expressive language skills. The severity of the impairment is determined by

- The age at which the hearing loss occurred
- The nature of the loss (its duration, the frequencies affected, and the degree)
- The susceptibilities of the individual child (eg, coexisting visual impairment, intellectual disability, primary language deficits, inadequate linguistic environment)

Children who have other sensory, linguistic, or cognitive deficiencies are affected most severely.

(See also Sudden Hearing Loss.)

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Pathophysiology of Hearing Loss

Hearing loss can be classified as conductive, sensorineural, or both (mixed loss).

Conductive hearing loss occurs secondary to lesions in the external auditory canal, tympanic membrane (TM), or middle ear. These lesions prevent sound from being effectively conducted to the inner ear.

Sensorineural hearing loss is caused by lesions of either the inner ear (sensory) or the auditory (8th) cranial nerve (neural). This distinction is important because sensory hearing loss is sometimes reversible and is seldom life threatening. A neural hearing loss is rarely recoverable and may be due to a potentially life-threatening brain tumor—commonly a cerebellopontine angle tumor. An additional type of sensorineural loss is termed **auditory neuropathy spectrum disorder**, when sound can be detected but the signal is not sent correctly to the brain, and is thought to be due to an abnormality of the inner hair cells or the neurons that innervate them within the cochlea (1).

Mixed loss may be caused by severe head injury with or without fracture of the skull or temporal bone, by chronic infection, or by one of many genetic disorders. It may also occur when a transient conductive hearing loss, commonly due to otitis media, is superimposed on a sensorineural hearing loss.

TABLE

Differences Between Sensory and Neural Hearing Losses

Test	Sensory Hearing Loss	Neural Hearing Loss
Speech discrimination	Moderate decrement	Severe decrement
Discrimination with increasing sound intensity	Usually improves up to a point, depending on the severity and distribution of loss of sensory elements	Deteriorates
Recruitment in which the perception of sound is exaggerated, especially at louder sound levels	Present	Absent
Acoustic reflex decay in which the acoustic reflex response is reduced over time during a measurement	Absent or mild	Present
Waveforms in auditory brain stem responses	Well formed with normal latencies for mild to moderate hearing losses; reduced for more severe losses	Absent or with abnormally long latencies
Otoacoustic emissions	Absent	Present

Pathophysiology reference

1. Pham NS: The management of pediatric hearing loss caused by auditory neuropathy spectrum disorder. *Curr Opin Otolaryngol Head Neck Surg* 25(5):396–399, 2017. doi: 10.1097/MOO.0000000000000390

Etiology of Hearing Loss

Hearing loss can be

Hearing Loss Myths

- Congenital (see table Congenital Causes of Hearing Loss) or acquired (see table Some Causes of Acquired Hearing Loss)
- Progressive or sudden
- Temporary or permanent
- Unilateral or bilateral
- Mild or profound

TABLE

Congenital Causes of Hearing Loss*

Anatomic Area Affected	Etiology†
Conductive	
External and middle ear	Genetic
	Developmental (eg, ossicular fixation)
	Idiopathic (unknown) malformation
	Drug-induced malformation (eg, with thalidomide)
Sensory	
Inner ear	Genetic
	Idiopathic (unknown) malformation
	Congenital infection (eg, rubella, cytomegalovirus infection, toxoplasmosis, syphilis)
	Rh incompatibility
	Anoxia
	Maternal ingestion of ototoxic medications (eg, for tuberculosis or severe infection)
	Drug-induced malformation (eg, with thalidomide)
Neural	
Central nervous system	Anoxia
	Idiopathic (unknown) malformation
	Genetic
	Congenital infection (eg, rubella, cytomegalovirus infection, toxoplasmosis, syphilis)
	Neurofibromatosis (type 2)
	Hyperbilirubinemia

* A number of congenital hearing losses may be mixed losses—a combination of conductive and sensory with or without a neural component

conductive and sensory with or without a neural component.

† Causes are listed in approximate order of greatest frequency first.

The **most common causes** of hearing loss overall are the following:

- Cerumen accumulation
- Noise
- Aging
- Infections (particularly among children and young adults)

TABLE

Some Causes of Acquired Hearing Loss

Cause*	Suggestive Findings	Diagnostic Approach†
External ear (conductive loss)		
Obstruction (eg, caused by cerumen, a foreign body, otitis externa, or, rarely, tumor)	Visible during examination	Otoscopy
Middle ear (conductive loss)		
Otitis media (secretory)	Hearing loss that may fluctuate Sometimes also dizziness, pain, or fullness in the ear Usually abnormal-looking TM Often a history of acute otitis media or other causative event	Otoscopy Tympanogram
Otitis media (chronic)‡	Chronic ear discharge Usually visible perforation Granulation tissue or polyp in the canal Sometimes cholesteatoma	Otoscopy For cholesteatoma, CT or MRI
Ear trauma‡	Apparent by history Often visible perforation of the TM, blood in the canal or behind the TM (if intact)	Otoscopy
Otosclerosis‡	Family history Age at onset in 20s to 30s Slowly progressive	Tympanogram

Tumors (benign and malignant)	Unilateral loss Often lesion visible during otoscopy	CT or MRI
Inner ear (sensory loss)		
Genetic disorders (eg, connexin 26 mutation, Waardenburg syndrome, Usher syndrome, Pendred syndrome)	Sometimes a positive family history (but usually negative) Consanguinity Connexin 26 mutations account for the vast majority of non-syndromic hearing loss cases and should be screened for initially Sometimes a white forelock of hair or different colored eyes suggests Waardenburg syndrome Loss of both vision and hearing can suggest Usher syndrome	Genetic testing CT and/or MRI
Autoimmune inner ear disease	Bilateral fluctuating or progressive hearing loss	Serologic testing (to rule out systemic rheumatic and other autoimmune disorders)
Noise exposure	Usually apparent by history	Clinical evaluation
Presbycusis	> 55 years in men, > 65 years in women Progressive, bilateral loss Normal neurologic examination	Clinical evaluation
Ototoxic medications (eg, aspirin, aminoglycosides,	History of use Bilateral loss	Clinical evaluation

vancomycin, cisplatinum, furosemide, ethacrynic acid, quinine)	Variable vestibular symptoms Renal failure	Blood tests to measure medication levels
Infections (eg, meningitis, purulent labyrinthitis)	Obvious history of infection Symptoms that begin during or shortly after an infection	Clinical evaluation
Systemic rheumatic disorders (eg, rheumatoid arthritis, systemic lupus erythematosus)	Joint inflammation, rash Sometimes a sudden change in vision or eye irritation Often known history of the disorder	Serologic testing
Meniere syndrome	Episodes of unilateral, fluctuating hearing loss accompanied by aural fullness, tinnitus, and vertigo	Gadolinium-enhanced MRI to rule out tumor
Barotrauma (with perilymphatic fistula)‡	History of abrupt pressure change (eg, scuba diving, rapid descent in airplane) or a blow to the ear canal Sometimes severe ear pain or vertigo	Tympanometry and balance function tests CT of temporal bone Surgical exploration if vertigo persists
Head trauma (with basilar skull fracture or cochlear concussion)‡	History of significant injury Possibly vestibular symptoms, facial weakness Sometimes blood behind the TM, CSF leak, ecchymosis over the mastoid	CT or MRI
Auditory neuropathy‡	Good sound detection, but poor word understanding	Auditory testing (auditory brain stem response [ABR], otoacoustic emissions)

		MRI
Central nervous system (neural loss)		
Tumors of the cerebellopontine angle (eg, vestibular schwannoma, meningioma)	Unilateral hearing loss, often with tinnitus Vestibular abnormalities Sometimes facial or trigeminal nerve deficits	Gadolinium-enhanced MRI
Demyelinating disease (eg, multiple sclerosis)	Unilateral loss Multifocal neurologic deficits Waxing and waning symptoms	MRI of the brain Sometimes lumbar puncture
* Each group is listed in approximate order of frequency.		
† All patients should have otoscopy and audiologic testing.		
‡ Mixed conductive and sensorineural loss may also be present.		
CSF = cerebrospinal fluid; TM = tympanic membrane.		

Cerumen (earwax) accumulation is the most common cause of treatable conductive hearing loss, especially in older patients (1). Foreign bodies obstructing the canal are sometimes a problem in children, both because of their presence and because of any damage inadvertently caused during their removal.

Noise can cause sudden or gradual sensorineural hearing loss. In acoustic trauma, hearing loss results from exposure to a single, extreme noise (eg, a nearby gunshot or explosion); some patients develop tinnitus as well. The loss is usually temporary (unless there is also blast damage, which may destroy the tympanic membrane, ossicles, or both). In noise-induced hearing loss, the loss develops over time because of chronic exposure to noise > 85 decibels (dB—see Sound Levels). Even before hearing loss can be documented, noise exposure can damage auditory neurons and their synapses on hair cells; this damage is referred to as "hidden hearing loss" or "synaptopathy," and patients may notice difficulty hearing in noisy environments and have accelerated age-related hearing loss (2). Although people vary

somewhat in susceptibility to noise-induced hearing loss, nearly everyone loses some hearing if they are exposed to sufficiently intense noise for an adequate time. Repeated exposure to loud noise ultimately results in loss of hair cells in the organ of Corti. Hearing loss typically occurs first at 4 kHz and gradually spreads to the lower and higher frequencies as exposure continues. In contrast to most other causes of sensorineural hearing loss, noise-induced hearing loss may be less severe at 8 kHz than at 4 kHz.

Aging, together with noise exposure and genetic factors, is a common risk factor for progressive decrease in hearing. Age-related hearing loss is termed presbycusis. Presbycusis is due to a combination of sensory cell (hair cell) and neuronal loss. Research also strongly suggests that early noise exposure accelerates age-related hearing loss (3). Higher frequencies are more affected than lower frequencies in age-related hearing loss.

Acute otitis media (AOM) is a common cause of transient mild to moderate hearing loss (mainly in children). However, without treatment, AOM sequelae and chronic otitis media (and the rarer purulent labyrinthitis) can cause permanent loss, particularly if a cholesteatoma forms.

Secretory otitis media (SOM) occurs in several ways. Almost all episodes of AOM are followed by a period of 2 to 4 weeks of SOM. SOM can also be caused by eustachian tube dysfunction (eg, resulting from cleft palate, benign or malignant tumors of the nasopharynx, or rapid changes in external air pressure as occur during descent from high altitudes or rapid ascent while scuba diving).

Systemic rheumatic and other autoimmune disorders can cause sensorineural hearing loss at all ages and can cause other symptoms and signs as well.

Autoimmune inner ear disease causes inflammation in the inner ear that results in a fluctuating or progressive bilateral hearing loss.

Ototoxic medications can cause sensorineural hearing loss, and many also have vestibular toxicity.

During the COVID-19 pandemic, many patients experienced an exacerbation of perceived hearing difficulty. The widespread wearing of masks by community members led to a reduced ability to read masked facial cues and lips. The muffling of speech sounds from masked speakers also contributed to perceived hearing difficulty.

TABLE

Sound Levels

Sound intensity and pressure (the physical correlates of loudness) are measured in decibels (dB). A dB is a unitless figure that compares 2 values and is defined as the logarithm of the ratio of a measured value to a reference value, multiplied by a constant:

$dB = k \log (V_{measured}/V_{ref})$

By convention, the reference value for sound pressure level (SPL) is taken as the quietest 1000-Hz sound detectable by young, healthy human ears.* The sound may be measured in terms of pressure (N/m^2) or intensity ($watts/m^2$).

Because sound intensity equals the square of sound pressure, the constant (k) for SPL is 20; for sound intensity, 10. Thus, each 20-dB increase represents a 10-fold increase in SPL but a 100-fold increase in sound intensity.

The dB values in the table below give only a rough idea of the risk of hearing loss. Some of them are dB SPL values (referenced to N/m^2), whereas others represent peak dB or dB on the A-scale (a scale that emphasizes the frequencies that are most hazardous to human hearing).

Db	Example
0	Faintest sound heard by human ear
30	Whisper, quiet library
60	Normal conversation, sewing machine, typewriter
90	Lawnmower, shop tools, truck traffic (90 dB for 8 hours a day is the maximum exposure without protection†)
100	Chain saw, pneumatic drill, snowmobile (2 hours a day is the maximum exposure without protection)
115	Sandblasting, loud concert, automobile horn (15 minutes a day is the maximum exposure without protection)
140	Gun muzzle blast, jet engine (noise causes pain and even brief exposure injures unprotected ears; injury may occur even with hearing protectors)
180	Rocket launching pad

* In audiometric testing, because human ears respond differently at different frequencies, the reference value changes for each frequency tested. Threshold values reported on

audiograms take this into account; the normal threshold is always 0 dB, regardless of the actual sound pressure level (SPL).

† This is the mandatory federal standard, but protection is recommended for more than brief exposure to sound levels > 85 dB.

Etiology references

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2. Liberman MC, Kujawa SG: Cochlear synaptopathy in acquired sensorineural hearing loss: manifestations and mechanisms. *Hear Res* 349:138-147, 2017. doi: 10.1016/j.heares.2017.01.003
3. Kujawa SG, Liberman MC: Acceleration of age-related hearing loss by early noise exposure: evidence of a misspent youth. *J Neurosci* 26(7):2115–2123, 2006. doi:10.1523/JNEUROSCI.4985-05.2006

Evaluation of Hearing Loss

Evaluation consists of detecting and quantifying hearing loss and determining etiology (particularly reversible causes).

Screening

Most adults and older children notice a sudden hearing loss, and caregivers may suspect that a neonate has a severe hearing loss within the first weeks of life when the neonate does not respond to voices or other sounds. However, progressive losses and nearly all losses in infants and young children must be detected by screening. Screening in children should begin at birth so that linguistic input can allow optimal language development. If screening is not done, severe bilateral losses may not be recognized until age 2 years, and mild to moderate bilateral or severe unilateral losses are often not recognized until children reach school age.

Screening in older adults should be considered because patients may not have noticed a gradual decline in hearing or may think it a normal consequence of aging.

Suspected hearing loss at any time should prompt referral to a specialist.

History

History of present illness should note how long hearing loss has been perceived, how it began (eg, gradual, acute), whether it is unilateral or bilateral, and whether sound is distorted (eg, music is off—dull or lifeless) or there is difficulty with speech discrimination. The patient should be asked whether the loss followed any acute event (eg, head injury, loud noise exposure, barotrauma [particularly a diving injury], or starting of a medication). Important accompanying symptoms include other otologic symptoms (eg, ear pain, tinnitus, ear discharge), vestibular symptoms (eg, disorientation in the dark, vertigo), and other neurologic symptoms (eg, headache, weakness or asymmetry of the face, an abnormal sense of taste, fullness of the ear). In children, important associated symptoms include presence of delays in speech or language development, visual changes, or delayed motor development.

Review of systems should seek to determine the impact of hearing difficulty on the patient's life.

Past medical history should note previous possibly causative disorders, including central nervous system infection, repeated ear infections, chronic exposure to loud noise, head trauma, systemic rheumatic disorders (eg, rheumatoid arthritis, lupus), and a family history of hearing loss. Medication history should specifically query current or previous use of ototoxic medications. For young children, a birth history should be sought to determine if there were any intrauterine infections or birth complications.

Physical examination

The focus is examination of the ears and hearing and the neurologic examination. The external ear is inspected for obstruction, infection, congenital malformations, and other lesions. The tympanic membrane (TM) is examined for perforation, drainage, otitis media (pus or fluid seen in the middle ear through the TM), and cholesteatoma. During the neurologic examination, particular attention needs to be paid to the 2nd through 7th cranial nerves as well as to vestibular and cerebellar function because abnormalities in these areas often occur with tumors of the brainstem and cerebellopontine angle. The Weber and Rinne tests require a tuning fork to differentiate conductive from sensorineural hearing loss.

In the **Weber test,** the stem of a vibrating 512-Hz or 1024-Hz tuning fork is placed on the midline of the head, and the patient indicates in which ear the tone is louder. In unilateral conductive hearing loss, the tone is louder in the ear with hearing loss. In unilateral sensorineural hearing loss, the tone is louder in the normal ear because the tuning fork stimulates both inner ears equally and the patient perceives the stimulus with the unaffected ear.

In the **Rinne test,** hearing by bone and by air conduction is compared. Bone conduction bypasses the external and middle ear and tests the integrity of the inner ear, 8th cranial nerve, and central auditory pathways. The stem of a vibrating tuning fork is held against the mastoid (for bone conduction); as soon as the sound is no longer perceived, the fork is removed from

the mastoid, and the still-vibrating tines are held close to the pinna (for air conduction). Normally, the fork can once more be heard, indicating that air conduction is better than bone conduction. With conductive hearing loss over 25 dB, the relationship is reversed; bone conduction is louder than air conduction. With sensorineural hearing loss, both air and bone conduction are reduced, but air conduction remains louder.

Red flags

Findings of particular concern are

- Unilateral sensorineural hearing loss
- Abnormalities of cranial nerves (other than hearing loss)
- Rapidly worsening or sudden hearing loss

Interpretation of findings

Many causes of hearing loss (eg, cerumen, injury, significant noise exposure, infectious sequelae, medications) are readily apparent based on results of the history and examination (see table Some Causes of Acquired Hearing Loss).

Associated findings are helpful in diagnosing the remaining small number of patients in whom no clear cause can be found. Patients who have focal neurologic abnormalities are of particular concern. The 5th or 7th cranial nerve or both are often affected by tumors that involve the 8th nerve, so loss of facial sensation and weak jaw clench (5th) and hemifacial weakness and taste abnormalities (7th) point to a lesion in that area. Signs of systemic rheumatic disorders (eg, joint swelling or pain, eye inflammation) or renal dysfunction may suggest these disorders as a cause. Maxillofacial malformations may suggest a genetic or developmental abnormality.

All children with delays in speech or language development or difficulty in school should be evaluated for hearing loss. Intellectual disability, aphasia, and autism spectrum disorder must also be considered. Delayed motor development may signal vestibular deficit, which is often associated with a sensorineural hearing loss.

Testing

Testing includes

- Audiologic tests
- Sometimes MRI or CT

Audiologic tests are required for all people who have hearing loss; these tests usually include

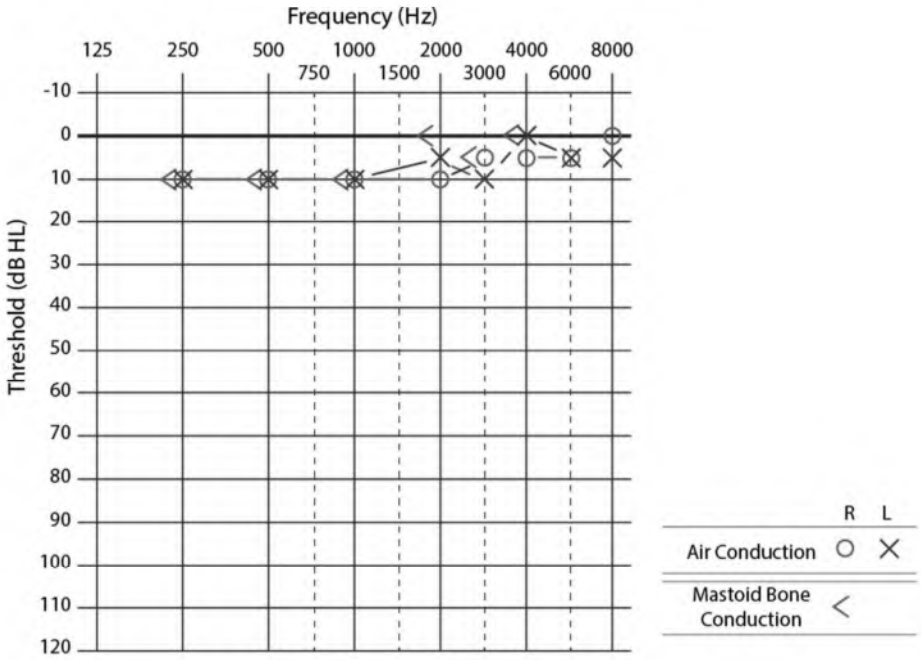
- Measurement of pure-tone thresholds with air and bone conduction
- Speech reception threshold
- Speech discrimination

- Tympanometry
- Acoustic reflex testing

Information gained from these tests helps determine whether more definitive differentiation of sensory from neural hearing loss is needed.

Pure-tone audiometry quantifies hearing loss. An audiometer delivers sounds of specific frequencies (pure tones) at different intensities to determine the patient's hearing threshold (how loud a sound must be to be perceived) for each frequency. Hearing in each ear is tested from 125 or 250 to 8000 Hz by air conduction (using earphones) and up to 4 kHz by bone conduction (using an oscillator in contact with the mastoid process or forehead). Test results are plotted on graphs called audiograms, which show the difference between the patient's hearing threshold and normal hearing at each frequency. The difference is measured in dB. The normal threshold is considered 0 dB hearing level (HI); hearing loss is considered present if the patient's threshold is > 20 dB HI. When hearing loss is such as to require loud test tones, intense tones presented to one ear may be heard in the other ear. In such cases, a masking sound, usually narrow band noise, is presented to the ear not being tested to isolate it.

Audiogram of Right Ear in a Patient with Normal Hearing



The vertical lines represent the frequencies that are tested from 125 to 8000 Hz. The horizontal lines record the threshold at which the patient states that the sound is heard.

Normal thresholds are 0 dB +/− 10 dB. Patients with a hearing threshold 20 dB or lower are considered to have normal hearing. The greater the dB, the louder is the sound and the worse the hearing.

"O" is the standard symbol for air conduction of the right ear; "X" is the standard symbol for air conduction for the left ear. The "<" is the standard symbol for unmasked bone conduction for the right ear (">" is the standard symbol for unmasked bone conduction of the left ear).

The reason why both masked and unmasked measures are needed is to make sure one ear is not hearing the sound presented to the other ear (one ear is "masked" so it does not hear the sound presented to the other ear, giving a false value). However, if air conduction is symmetric, only unilateral unmasked bone conduction need be done.

Image courtesy of Mickie Hamiter, MD.

Speech audiometry includes the speech reception threshold (SRT) and the word recognition score. The SRT is a measure of the intensity at which speech is recognized. To determine the SRT, the examiner presents the patient with a list of words at specific sound intensities. These words usually have 2 equally accented syllables (spondees), such as "railroad," "staircase," and "baseball." The examiner notes the intensity at which the patient repeats 50% of the words correctly. The SRT approximates the average hearing level at speech frequencies (eg, 500 Hz, 1000 Hz, 2000 Hz).

The **word recognition score** tests the ability to discriminate among the various speech sounds or phonemes. It is determined by presenting 50 phonetically balanced one-syllable words at an intensity of 35 to 40 dB above the patient's SRT. The word list contains phonemes in the same relative frequency found in conversational English. The score is the percentage of words correctly repeated by the patient and reflects the ability to understand speech under optimal listening conditions. A normal score ranges from 90 to 100%. The word recognition score is normal with conductive hearing loss, albeit at a higher intensity level, but can be reduced at all intensity levels with sensorineural hearing loss. Discrimination is even poorer in neural than in sensory hearing loss. Testing of words understood within full sentences is another type of recognition test that is often used to assess candidacy for implantable devices (when the benefit from hearing aids is insufficient).

Tympanometry measures the impedance of the middle ear to acoustic energy and does not require patient participation. It is commonly used to screen children for middle ear effusions. A probe containing a sound source, microphone, and air pressure regulator is placed snugly with an airtight seal into the ear canal. The probe microphone records the reflected sound from the tympanic membrane (TM) while pressure in the canal is varied. Normally, maximal compliance of the middle ear occurs when the pressure in the ear canal equals atmospheric pressure.

Abnormal compliance patterns suggest specific anatomic disruptions. In eustachian tube obstruction and middle ear effusion, maximal compliance occurs with a negative pressure in the ear canal. When the ossicular chain is disrupted, as in necrosis or dislocation of the long process of the incus, the middle ear is excessively compliant. When the ossicular chain is fixed, as in stapedial ankylosis in otosclerosis, compliance may be normal or reduced.

The **acoustic reflex** is contraction of the stapedius muscle in response to loud sounds, which changes the compliance of the TM, protecting the middle ear from acoustic trauma. The reflex is tested by presenting a tone and measuring what intensity provokes a change in middle ear impedance as noted by movement of the TM. An absent reflex could indicate middle ear disease or a tumor of the auditory nerve. Any conductive hearing loss abolishes the acoustic reflex. Additionally, facial paralysis abolishes the reflex because the facial nerve innervates the stapedius muscle.

Advanced testing is sometimes needed. Gadolinium-enhanced MRI of the head to detect lesions of the cerebellopontine angle may be needed in patients with an abnormal neurologic examination or those whose audiologic testing shows poor word recognition, asymmetric sensorineural hearing loss, or a combination when the etiology is not clear.

CT is done if bony tumors or bony erosion is suspected. Magnetic resonance angiography and venography is done if vascular abnormalities such as glomus tumors are suspected.

The **auditory brain stem response** uses surface electrodes to monitor brain wave response to acoustic stimulation in people who cannot otherwise respond.

Electrocochleography measures the activity of the cochlea and the auditory nerve with an electrode placed on or through the eardrum. It can be used in Meniere disease to support diagnosis and monitor response to treatment, can be used in patients who are awake, and is useful in intraoperative monitoring.

Otoacoustic emissions testing measures sounds produced by outer hair cells of the cochlea in response to a sound stimulus usually placed in the ear canal. These emissions are essentially low-intensity echoes that occur with cochlear outer hair cell activation. Emissions are used to screen neonates and infants for hearing loss and to monitor the hearing of patients who are using ototoxic medications (eg, gentamicin, cisplatin).

Central auditory evaluation measures discrimination of degraded or distorted speech, discrimination in the presence of a competing message in the opposite ear, the ability to fuse incomplete or partial messages delivered to each ear into a meaningful message, and the capacity to localize sound in space when acoustic stimuli are delivered simultaneously to both ears. This testing should be done on certain patients, such as children with a reading or other learning problem and older adults who seem to hear but do not comprehend.

In children with hearing loss, additional testing should include an ophthalmologic examination because many genetic causes of deafness also cause ocular abnormalities. Children with unexplained hearing loss should also have an ECG to look for long QT syndrome and possibly also genetic testing.

Treatment of Hearing Loss

The causes of a hearing loss should be determined and treated.

Ototoxic medications should be stopped or the dose should be lowered unless the severity of the disease being treated (usually cancer or a severe infection) requires that the risk of additional ototoxic hearing loss be accepted. Attention to peak and trough medication levels is mandatory to help minimize risk and should be obtained in all patients. In patients with renal dysfunction, adjustments to medication dosages with close attention to peak and trough levels are required to minimize the risk of ototoxicity (eg, see dosing considerations for aminoglycoside antibiotics). There are some genetic abnormalities involving the mitochondria that increase the sensitivity to aminoglycoside antibiotics, and these can be identified with genetic screening.

Fluid from middle ear effusion can be drained by myringotomy and prevented from reaccumulating with the insertion of a tympanostomy tube. Benign growths (eg, enlarged adenoids, nasal polyps) and malignant tumors (eg, nasopharyngeal cancers, sinus cancers) blocking the eustachian tube or ear canal can be removed. Hearing loss caused by autoimmune or systemic rheumatic disorders may respond to corticosteroids.

Damage to the tympanic membrane or ossicles or otosclerosis may require reconstructive surgery (eg, tympanoplasty with ossicular chain reconstruction, ossiculoplasty). Brain tumors causing hearing loss may in some cases be removed or radiated and hearing preserved.

Many causes of hearing loss have no cure, and treatment involves compensating for the hearing loss with hearing aids and, for severe to profound loss, a cochlear implant. In addition, various coping mechanisms may help.

Hearing aids

Amplification of sound with a hearing aid helps many people. Although hearing aids do not restore hearing to normal, they can significantly improve communication. Advances in amplification circuits provide a more natural, tonal quality to amplified sound and offer features of "smart," responsive amplification that takes into account the listening environment (eg, in noise-challenging and multi-talker environments). Physicians should encourage hearing aid use and help patients overcome a sense of social stigma that continues to obstruct use of these devices, perhaps by making the analogy that a hearing aid is to hearing as eye glasses

are to seeing. Other factors that limit more widespread hearing aid use include cost and comfort issues.

All hearing aids have a microphone, amplifier, speaker, earpiece, and volume control, although they differ in the location of these components. Over-the-counter hearing aids are available with the benefit of lower cost. However, unlike with traditional hearing aids, users do not get the benefit of working with an audiologist to customize the amplification to individual hearing loss frequencies or fit of the ear canal. Over-the-counter hearing aids are only suitable for mild to moderate hearing losses.

The best models are adjusted to a person's particular pattern of hearing loss. For example, people with mainly high-frequency hearing loss might not benefit from simple amplification, which merely makes the garbled speech they hear sound louder; they usually need a hearing aid that selectively amplifies the high frequencies. Some hearing aids contain vents in the ear mold, which facilitate the passage of high-frequency sound waves. Some use digital sound processing with multiple frequency channels so that amplification more precisely matches hearing loss as measured on the audiogram.

Telephone use can be difficult for people with hearing aids. Typical hearing aids cause squealing when the ear is placed next to the phone handle. Some hearing aids have a phone coil with a switch that turns the microphone off and links the phone coil electromagnetically to the speaker magnet in the phone or uses a bluetooth connection (both landline and mobile phones).

For moderate to severe hearing loss, a postauricular (ear-level) aid, which fits behind the pinna and is coupled to the ear mold with flexible tubing, is appropriate. An in-the-ear aid is contained entirely within the ear mold and fits less conspicuously into the concha and ear canal; it is appropriate for mild to moderate hearing loss. Some people with mild hearing loss limited to high frequencies are most comfortably fitted with postauricular aids and completely open ear canals. Canal aids are contained entirely within the ear canal and are cosmetically acceptable to many people who would otherwise refuse to use a hearing aid, but they are difficult for some people (especially older adults) to manipulate.

The **CROS aid** (contralateral routing of signals) is occasionally used for severe unilateral hearing loss; a hearing-aid microphone is placed in the nonfunctioning ear, and sound is routed to the functioning ear through a wire or radio transmitter. This device enables the wearer to hear sounds from the nonfunctioning side, allowing for some limited capacity to localize sound. If the better ear also has some hearing loss, the sound from both sides can be amplified with the binaural CROS (BiCROS) aid.

The body aid type is appropriate for profound hearing loss. It is worn in a shirt pocket or a body harness and connected by a wire to the earpiece (the receiver), which is coupled to the

ear canal by a plastic insert (ear mold).

A **bone conduction aid** may be used when an ear mold or tube cannot be used, as in atresia of the ear canal or persistent otorrhea. An oscillator is held against the head, usually over the mastoid, with a spring band, and sound is conducted through the skull to the cochlea. Bone conduction hearing aids require more power, introduce more distortion, and are less comfortable to wear than air conduction hearing aids. Some bone conduction aids (bone-anchored hearing aids or BAHAs) are surgically implanted in the mastoid process, avoiding the discomfort and prominence of the spring band.

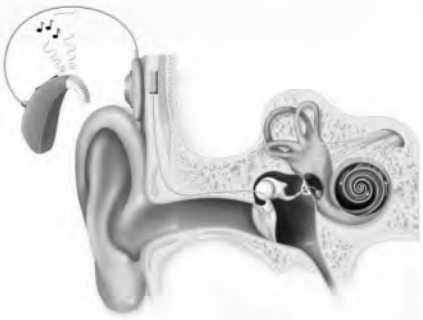
Cochlear implants

Patients with advanced levels of hearing loss, including those with some residual (natural) hearing but who even with a hearing aid cannot understand more than half of the words contained in connected speech, may benefit from a cochlear implant. The surgery may result in loss of some residual hearing. However, even if residual hearing is lost, cochlear implants can greatly improve hearing, even in people who are profoundly deaf.

This device provides electrical signals directly into the auditory nerve via multiple electrodes implanted in the cochlea. An external microphone and processor convert sound waves to electrical impulses, which are transmitted through the skin electromagnetically from an external induction coil to an internal coil implanted in the skull above and behind the ear. The internal coil connects to electrodes inserted in the scala tympani.

Cochlear Implant

IMAGE



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Cochlear implants help with speech-reading by providing information about the intonation of words and the rhythm of speech. Many if not most adults with cochlear implants can discriminate words without visual clues, allowing them to talk on the telephone. Cochlear implants enable deaf people to hear and distinguish environmental sounds and warning signals. They also help deaf people modulate their voice and make their speech more intelligible.

Outcomes with cochlear implants vary, depending on a number of factors, including the

- Length of time between onset of hearing loss and placement of the implant (shorter duration leads to better outcomes)
- Cause of the underlying hearing loss

- Position of the implant within the cochlea

Brain stem implants

Although cochlear implants are not an option for patients who have had both acoustic nerves destroyed (eg, by bilateral temporal bone fractures or neurofibromatosis) or are born without cochlear nerves, these patients can have some hearing restored by means of brain stem implants that have electrodes connected to sound-detecting and sound-processing devices similar to those used for cochlear implants, although usually not as good. In general, children born without cochlear nerves who receive the brain stem implant tend to have more hearing restored than patients who receive it following vestibular neuroma resection. Results of the brain stem implant range from assistance with lip-reading skills to the ability to understand language without lip-reading (termed "open-set speech" understanding).

Assistive strategies and technologies

Alerting systems that use light let people know when the doorbell is ringing, a smoke detector is sounding, or a baby is crying. Special sound systems transmitting infrared or FM radio signals help people hear in theaters, churches, or other places where competing noise exists. Many television programs carry closed captioning. Telephone communication devices are also available.

Lip-reading or speech-reading is particularly important for people who can hear but have trouble discriminating sounds. Most people get useful speech information from lip-reading even without formal training. Even people with normal hearing can better understand speech in a noisy place if they can see the speaker. To use this information, the listener must be able to see the speaker's mouth. Health care personnel should be sensitive to this issue and always position themselves appropriately when speaking to the hearing-impaired. Observing the position of a speaker's lips allows recognition of the consonant being spoken, thereby improving speech comprehension in patients with high-frequency hearing loss. Lip-reading may be learned in aural rehabilitation sessions in which a group of age-matched peers meets regularly for instruction and supervised practice in optimizing communication.

People can **gain control over their listening environment** by modifying or avoiding difficult situations. For example, people can visit a restaurant during off-peak hours, when it is quieter. They can ask for a booth, which blocks out some extraneous sounds. In direct conversations, people may ask the speaker to face them. At the beginning of a telephone conversation, they can identify themselves as being hearing-impaired. At a conference, the speaker can be asked to use an assistive listening system, which makes use of either inductive loop, infrared, or FM technology that sends sound through the microphone to a patient's hearing aid.

People with profound hearing loss often communicate by using **sign language**. American Sign Language (ASL) is the most common version in the United States. Other forms of linguistic

communication that utilize visual inputs include Signed English, Signing Exact English, and Cued Speech. Around the world, it has been estimated that there are over 300 unique sign languages, with different countries, cultures, and villages having their own unique form of sign language.

Single-Sided Deafness

Patients with single-sided deafness (SSD) represent a special challenge. In one-on-one situations, hearing and speech understanding is relatively unaffected. However, with noisy backgrounds or complex acoustic environments (eg, classrooms, parties, meetings), patients with SSD are unable to hear and communicate effectively. Further, patients who hear out of only one ear are unable to localize the origin of sounds. The "head shadow" effect is the skull's ability to block sound coming from the deaf side from reaching the hearing ear. This can result in up to a 30-dB loss of sound energy reaching the hearing ear (as a comparison, a store-bought ear plug results in a 22- to 32-dB drop in hearing, roughly equivalent). For many patients, SSD can be life-altering and lead to significant disability at work and socially.

Treatment for SSD includes contralateral routing of signal (CROS) hearing aids or bone-anchored hearing implants that pick up sound from the deaf side and transfer it to the hearing ear without the loss of sound energy. Although these technologies improve hearing in noisy settings, they do not allow sound localization. Cochlear implants are increasingly being used with success in patients with SSD, particularly if the deaf ear also has severe tinnitus; implants have also been shown to provide sound localization.

Treatment of Hearing Loss in Children

In addition to treatment of any cause and the provision of hearing aids, children with hearing loss require support of language development with appropriate therapy. Because children must hear language to learn it spontaneously, most deaf children develop language only with special training, ideally beginning as soon as the hearing loss is identified (an exception would be a deaf child growing up with deaf parents who are fluent sign language users). Deaf infants must be provided with a form of language input. For example, a visually based sign language can provide a foundation for later development of oral language if a cochlear implant is not available. However, for children, there is no substitute for access to the sounds of speech (phonemes) to enable them to integrate acoustic inputs and develop a refined and nuanced understanding of speech and language.

If infants as young as 1 month have profound bilateral hearing loss and cannot benefit from hearing aids, they can be candidates for a cochlear implant. Although cochlear implants allow auditory communication in many children with either congenital or acquired deafness, they are

generally more effective in children who already have developed language. Children who have postmeningitic deafness eventually develop an ossified inner ear that prevents the placement of an implant; they should receive cochlear implants as soon as possible to allow the implant to be correctly placed and maximize effectiveness. Children whose acoustic nerves have been destroyed by tumors may be helped by implantation of brain stem auditory-stimulating electrodes. Children with cochlear implants may have a slightly greater risk of meningitis than children without cochlear implants or adults with cochlear implants.

Children with unilateral deafness should be allowed to use a special system in the classroom, such as an FM auditory trainer. With these systems, the teacher speaks into a microphone that sends signals to a hearing aid in the child's nonaffected ear, improving the child's greatly impaired ability to hear speech against a noisy background.

Prevention of Hearing Loss

Prevention of hearing loss consists mainly of limiting duration and intensity of noise exposure. People required to expose themselves to loud noise must wear ear protectors (eg, plastic plugs in the ear canals or glycerin-filled muffs over the ears). The Occupational Safety and Health Administration (OSHA) of the U.S. Department of Labor and similar agencies in many other countries have standards regarding the length of time that a person can be exposed to a noise (see OSHA's occupational noise exposure standards). The louder the noise, the shorter the permissible time of exposure.

Use of ototoxic medications should be avoided when feasible. Risk of ototoxicity is not clearly lower with once-daily dosing of aminoglycosides than with more frequent dosing intervals (1).

Prevention reference

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Geriatrics Essentials: Hearing Loss

Older adults typically experience a progressive decrease in hearing (presbycusis). In the United States, 22% of people ages 65 to 74 years and 55% of those who are 75 and older have disabling hearing loss (1). Although hearing loss is common with aging, hearing loss in older adults should be evaluated and not ascribed simply to aging; older patients may have a tumor, a neurologic or autoimmune or systemic rheumatic disorder, or an easily correctable conductive hearing loss. Also, research strongly suggests that hearing loss in older adults can facilitate dementia (2), which may be mitigated by properly correcting hearing loss.

Presbycusis

Presbycusis is sensorineural hearing loss that probably results from a combination of age-related deterioration and cell death in various components of the hearing system and the effects of chronic noise exposure.

Hearing loss usually affects the highest frequencies (18 to 20 kHz) early on and gradually affects the lower frequencies; it usually becomes clinically significant when it affects the critical 2- to 4-kHz range at about age 55 to 65 years (sometimes sooner). The loss of high-frequency hearing significantly affects speech comprehension. Although the loudness of speech seems normal, certain consonant sounds (eg, C, D, K, P, S, T) become harder to hear. Consonant sounds are the most important sounds for speech recognition. For example, when "shoe," "blue," "true," "too," or "new" is spoken, many people with presbycusis can hear the "oo" sound, but most have difficulty recognizing which word has been spoken because they cannot distinguish the consonants. This inability to distinguish consonants causes affected people to often think the speaker is mumbling. A speaker attempting to speak louder usually accentuates vowel sounds (which are low frequency), doing little to improve speech recognition. Speech comprehension is particularly difficult when background noise is present.

Screening

A screening tool is often helpful for older adults because many do not realize they have hearing loss. One tool is the Hearing Handicap Inventory for the Elderly–Screening Version, which asks

- Does a hearing problem cause you to feel embarrassed when you meet people?
- Does a hearing problem cause you to feel frustrated when talking to a family member?
- Do you have difficulty hearing when someone whispers?
- Do you feel handicapped by a hearing problem?
- Does a hearing problem cause you difficulty when visiting friends, relatives, or neighbors?
- Does a hearing problem cause you to attend religious services less often than you would like?
- Does a hearing problem cause you to have arguments with family members?
- Does a hearing problem cause you difficulty when listening to the television or radio?
- Do you feel that any difficulty with your hearing hampers your personal or social life?
- Does a hearing problem cause you difficulty when in a restaurant with relatives or friends?

Scoring is "no" = 0 points, "sometimes" = 2 points, and "yes" = 4 points. Scores > 10 suggest significant hearing impairment and necessitate follow-up (3).

Geriatrics essentials references

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Key Points

- **Cerumen, genetic disorders, infections, aging, and noise exposure are the most common causes of hearing loss.**
- **All patients with hearing loss should have audiologic testing.**
- **Cranial nerve deficits and other neurologic deficits should raise concern and warrant imaging tests.**
- **Treatment modalities include correction of reversible causes, hearing aids, surgical procedures including ossicular reconstruction and cochlear implants, and various assistive technologies.**

More Information

The following English-language resources may be useful. Please note that THE MANUAL is not responsible for the content of these resources.

National Institute on Deafness and Other Communication Disorders: Information for patients and providers regarding hearing loss and other communication disorders, spanning functions of hearing, balance, taste, smell, voice, speech, and language
Center for Disease Control and Prevention—Hearing Loss in Children: Information for parents about programs and services for children with hearing loss
The National Institute for Occupational Safety and Health (NIOSH)—Noise and Hearing Loss Prevention: Reviews occupational regulations and standards, noise control strategies, and hearing protective devices, as well as hearing loss prevention programs, risk factors, and information for specific industries and occupations

Drugs Mentioned In This Article

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MMR MILITARY MEDICAL RESEARCH

REVIEW Open Access

Impact of noise on hearing in the military

Jenica Su-ern Yong* and De-Yun Wang

Abstract

Hearing plays a vital role in the performance of a soldier and is important for speech processing. Noise-induced hearing loss is a significant impairment in the military and can affect combat performance. Military personnel are constantly exposed to high levels of noise and it is not surprising that noise induced hearing loss and tinnitus remain the second most prevalent service-connected disabilities. Much of the noise experienced by military personnel exceeds that of maximum protection achievable with double hearing protection. Unfortunately, unlike civilian personnel, military personnel have little option but to remain in noisy environments in order to complete specific tasks and missions. Use of hearing protection devices and follow-up audiological tests have become the mainstay of prevention of noise-induced hearing loss. This review focuses on sources of noise within the military, pathophysiology and management of patients with noise induced hearing loss.

Keywords: Hearing loss, Noise-induced, Military personnel, Ear protective devices

Introduction

Noise-induced hearing loss is a major preventable disease. It can be caused by an acute exposure to an intense impulse of sound or by a continuous steady-state long-term exposure with sound pressure levels higher than 75–85 dB (Table 1).

Noise remains a large public health problem with an estimated 1.3 billion people being affected by hearing loss [1]. It ranks 13th globally as the cause of years lived with disability (YLD). YLD is estimated by multiplying the number of incident cases in that period with the duration of disease and the weight factor which measures disease severity. In North America, it ranks 19th as the cause of YLD, in Central Asia, it ranks 15th and in Southeast Asia it ranks 9th.

The prevalence of hearing loss and tinnitus in military population are greater than in the general public. Almost every soldier, sailor, airman or marine will be exposed to hazardous noise levels at some point in their career [2-4]. The two most prevalent service connected disabilities for veterans in the United States at the end of fiscal year 2012 remain tinnitus and hearing loss, with tinnitus affecting 115,638 veterans (9.7%) and hearing loss affecting 69,326 veterans (5.8%) [5]. In Finland, despite the increasing use of hearing protection devices, a large proportion of professional soldiers experience disabling tinnitus and hearing loss [6].

Hearing acuity is a key component of a soldier's effectiveness in the battlefield. The presence of tinnitus and hearing loss can significantly impair a soldier's ability to hear important acoustic cues or communication signals from the unit or the enemy [2]. Hearing problems can also be a reason for disruption of their military service. In a study by Muhr et al., 33 soldiers (3.9%) had interrupted training as a result of their hearing problems [7].

Review

Sources of noise-induced hearing loss

Land force

Sources of noise within the military vary with soldier's designation. Within the Belgian military, Fighting in Built-Up Area (FIBUA) training, shooting with large calibre weapons and participation in military exercises were the strongest determinants of hearing loss [4].

Within the infantry, weapons emit high levels of noise. Table 2 depicts the amount of permissible noise allowed and Table 3 depicts the typical noise level emitted by different weapons. Many weapons emit sounds that exceed the maximum achievable protection that double hearing protection can offer. Double hearing protection means both earmuffs and ear plugs are used. The US Department of Defense published a medical surveillance monthly report on noise-induced hearing loss and it was found that

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Table 1 Glossary of terms used

Terms	Descrption
Sound pressure level (SPL)	Sound intensity is expresses the pressure caused by a sound wave and is indicated by sound pressure level. The unit of measurement is the decibel (dB SPL)
dB Scale	A logarithmic scale to measure sound pressure level
dBA	To measure noise, A-weighted SPL (dBA) can be used. In contrast to SPL which represents a physical dimension, A-weighted SPL represents a perceptual dimension. The dB SPL will be different from dBA for different for different frequencies as low frequency sounds and high frequency sounds tend to be less loud than mid-frequency sounds
L_{Aeq}	This refers to the average level of sound pressure within a certain time period with the A-filter used for frequency weighting. The A-filter is a frequency-weighting of sound pressure levels that mimics the sensitivity of the auditory system of humans (eg, low-frequency sounds contribute little to the A-weighted dB level)

noise-induced hearing injuries were more prevalent among combat-specific occupations (41.2 per 1000 person-years of active component military service) [8].

Navy

In the Navy, the highest indoor noise levels were found in engine rooms [9,10]. Landing ship tanks and patrol vessels typically generated about 98 to 103 dBA of noise, whereas the noise level in missile gun boats were at 120 dBA [9]. The loudest noise generated is on the carrier decks that can range from 130 to 160 dBA [2].

Air force

Military aircraft personnel are not spared, the average noise experienced in service helicopters was found to be 97 dBA for 'Gazelle', 99.8 dBA for the 'Scout', 99.9 dBA for the 'Puma' and 100 dBA for the 'Lynx' [11]. In fighter planes, the noise level ranged from 97 to 104 dBA, in jet trainers the noise level was at 100 to 106 dBA and in transporter aircrafts, the noise level was found to be between 88 to 101 dBA [12]. In such settings, due to chronic noise exposure, pilots were found to exhibit hearing impairment [13].

Table 2 Amount of permissible noise exposure allowed in theworkplace*

Duration per day (hour)	Sound level (dBA)
8	90
6	92
4	95
3	97
2	100
1 ½	102
1	105
½	110
¼ or less	115

*Adapted from OSHA 2014. Standards. US Dept Labor: Occupational Noise Exposure [Online]. vailable by Occupational Safety and Health Administration. https://www.osha.gov/SLTC/noisehearingconservation/index.html.

Pathophysiology

Injury from noise can occur in 2 main ways. First, high level, short duration exposure exceeding more than 140 dB can cause the delicate inner ear tissues to beyond stretch beyond their elastic limits. This causes mechanical disruption of the sterocilia and direct damage to supporting and sensory cells [14]. In such cases, the maximum sound pressure level (SPL) is more important than the duration of the exposure [15]. This type of acoustic trauma can result in immediate and permanent hearing loss.

Second, long term exposure to low level noise damages the cochlea metabolically rather than mechanically. It involves biochemical pathways leading to cell death either through apoptosis or necrosis [16]. There are 2 factors that influence which cell death pathway is activated. The first factor is the sound intensity level. Noises of 105 dB favour necrosis whereas louder noises (120 dB) favour apoptosis [17]. Another factor is the time between noise exposure and morphological analysis. Outer hair cells immediately start dying during the initial acoustic insult and continue to do so for at least 30 days after the event [18,19]. Immediately after the insult, apoptosis is the main cause of cell death. After 4 days, the apoptotic activities start to diminish and by day 30 both apoptosis and cell necrosis contribute equally to cell death [19,20].

Exposure to intense sound can cause auditory thresholds to become elevated permanently or temporarily. Reversible hearing loss is referred to as temporary threshold shift (TTS). Depending on duration of exposure, recovery from TTS can occur over a period of minutes to hours or days. If TTS does not recover, permanent hearing loss results and this is referred to permanent threshold shift (PTS) [21]. These two phenomena, permanent and temporary threshold shifts are still not well understood.

PTSs are postulated to be either due to direct mechanical trauma or metabolic overstimulation of cellular elements within the organ of Corti which is associated with generation of reactive oxygen species [22].

Various mechanisms have been proposed for TTS and include synaptic fatigue, metabolic fatigue of either stria vascularis or hair cells and changes in cochlear blood flow. An important component of noise-induced hearing loss is postsynaptic damage in the afferent dendrites beneath the inner hair cells [23]. Even though hair cells recover normal function, there is rapid extensive and

Table 3 Peak sound pressure level range of different weapons*

Type of weapons	Peak sound pressure level range (dB)
Rifles	
.45-70 Rifle	155.2-159.9
.30-06 Rifle	158.7-163.1
Shotguns	
.410 Bore	151.0- 157.3
20 Gauge	154.8
12 Gauge	156.1- 161.5
Pistols	
.22	151
9 mm Luger	159 163
.45 ACP	158
Other Weapons	
Hand grenade	158
Light anti-tank weapon	184
Inside armored vehicle, continuous noise	L_{Aeq}103 – 107

*Adapted from Chen L, Brueck SE. Noise and lead exposure at an outdoor firing range – California. Health Hazard Evaluation report Sept 2011, and from Kramer WL. Gunfire noise and hearing. American Tinnitus Association. June 2002:14–15.

irreversible loss of synapses and delayed and progressive loss of cochlear neurons over many months [24,25]. This resultant cochlear neuropathy has been observed in mice exposed to just 84 dB SPL over a week [26]. It is possible that many people with difficulty in hearing also suffer from noise-induced cochlear neuropathy seen in animal studies.

Noise not only increases hearing threshold, but it can also cause tinnitus and hyperacusis. This can be present in individuals with normal hearing thresholds but with cochlear neuropathy. Indeed, studies have shown that patients with tinnitus have evidence of reduced Wave I at high sound levels [25,27]. The pathogenesis of tinnitus is postulated to be due to a compensatory increase in neural gain to the auditory brainstem as a result of reduced neural output from cochlea [27,28]. The gain can lead to tinnitus due to the amplification of spontaneous activity of auditory neurons.

Clinical presentation

Symptoms and signs

Exposure to noise can induce several hearing symptoms such as temporary threshold shifts (TTS), tinnitus, hyperacusis, recruitment, distortion or abnormal pitch perception [29]. Tinnitus can occur in the presence or absence of an abnormal audiogram. The tinnitus pitch match is associated with the frequency spectrum of hearing loss [30,31].

Patients may exhibit difficulty in listening to high frequency noise such as whistles or buzzers. They may also have difficulty differentiating some speech consonants, especially if they are in areas where there is significant background noise.

However these symptoms are typically insidious and most patients with noise induced hearing loss may not notice their deficiency until it starts to affect communication.

Audiometric characteristics

Noise-induced deafness usually occurs at high frequencies with hearing loss beginning around 4 kHz or 6 kHz. However, as the disease progresses, hearing loss will also be seen at the lower frequencies. The expected maximal changes in thresholds are predictable at one-half octave above maximal frequency of the exposure [32].

The audiometric pattern in noise induced hearing loss is usually symmetrical and bilateral. However some asymmetry is not unexpected. The asymmetry in hearing threshold may be partly explained by the position of head during work [33]. Hong et al. studied workers in the American construction industry and it was found that the left ear predominantly experienced more hearing loss than the right. Asymmetry was postulated to be due to the work habit that the operators look over their right shoulder when operating heavy equipment, exposing their left ear to the noise generated by the machines [34]. Hearing loss among rifle shooters also tend to be asymmetrical, as hearing in the ear closest to the barrel tends to be worse as it is closer to the explosion whereas the other ear is protected by the head [12,35]. In the civilian population, this was also seen in musicians who played high string instruments where the left ear was found to be exposed to 4.6 dB more than the right ear [36].

Management of patients

Noise prevention

Within the military setting, noise exposure may be controlled through isolation (distance and physical barriers), vibration dampening, insulation and proper equipment maintenance [37]. The preferred method of preventing noise induced hearing loss and noise induced tinnitus is engineering controls. Other methods including the use of hearing protection devices such as foam ear plugs, molded insets and sound attenuating ear muffs are limited and can diminish perception of speech. Prevention is also reliant on the individual's compliance to the sound protection devices.

Currently, the Navy considers 85dBA to be the threshold for single hearing protection and 104 dBA for double hearing protection for steady state noise settings [38]. Noise levels on the flight deck during flight and some aircraft maintenance operations are intense and can

easily exceed the 104 dBA threshold for double hearing protection [2].

In the British Army Air Corps, pilots of the Lynx have to wear the Mk4 flying helmet and pilots of the Apache wear the Integrated Helmet and Display Sighting System (IHADSS). Circumaural earmuffs are integrated into the aircrew helmet system. Lang *et al.* found that hearing was better than predicted in nearly all frequencies for both ears for both Lynx and Apache pilots, demonstrating that the circumaural earmuffs implemented reduce the risk of noise induced hearing loss [39].

Even the best hearing protection equipment will be ineffective if it is not used properly or if soldiers are not compliant. A focus group study found that main concerns with hearing protection were interference with detection and localization of auditory warning and perception of orders [40]. Bjorn *et al.* conducted a study on the hearing protection equipment use by the crew on the flight deck and found that 79% of flight deck personnel received an estimated 0–6 dB rather than the expected 28–30 dB of noise attenuation from either misuse of earplugs or non-compliance to ear plugs [41].

Pharmacotherapy

Currently there is no established treatment for patients and it is limited to prevention and follow-up. However recent clinical trials have proved promising.

Magnesium

Magnesium efficacy was tested in a double-blind study. Test subjects were given either 122 mg of magnesium or a placebo for 10 days and thereafter subjected monoaurally to 90 dB SPL of white noise for 10 minutes. TTS of > 20 dB was found in 28% of the placebo group compared to 12% in the magnesium-supplemented group [42].

Attias *et al.* conducted a double-blind placebo controlled study on army recruits and concluded that recruits who had magnesium supplementation had less frequent noise-induced PTS compared to the placebo group [43]. These 300 army recruits underwent basic military training where they were subjected to shooting range noises of an average peak level of 164 dBA and <1 ms duration with the use of ear plugs which reduced noise level by about 25 dBA. PTS was defined as a threshold >25 dB hearing loss in at least 1 frequency and it was found that PTS was higher in placebo group (11.5%) as opposed to the participants in the magnesium group (1.2%).

N-acetyl-cysteine (NAC)

NAC acts as a reactive oxygen species scavenger and is postulated to reduce noise-induced hearing loss by reducing the exposure of the cochlea to reactive oxygen species. Glutathione S-transferases (GST) are a family of detoxification enzymes which help cells resist oxidative injury. Glutathione detoxification can be affected in individuals with genetic polymorphisms involving deletion of base pairs in the genes like GSTT1 and GSTM1. Patients with these two high-risk genotypes are more prone to have oxidative injury from noise induced hearing loss [44,45]. In a trial conducted on steel manufacturing workers, employees were administered either 1200 mg of NAC or placebo. Trial was conducted in a 2 × 2 crossover design with subjects taking either NAC or placebo for 14 days and with a 14-day wash-out period between treatments. Noise exposure was 88.4 - 89.4 dB as assessed by personal noise monitoring. The difference between the TTS was not found to be significant. However, when the subjects were subdivided based on genetic polymorphisms or GSTT1 and GSTM1, the subgroup with null genotypes in both GSTT1 and GSTM1 experienced protection by NAC [46].

Methionine (MET)

Another glutathione (GSH) precursor is MET, an essential amino acid that can be converted to cysteine, which is the rate-limiting substrate for GSH production. It has been shown in animal studies to be otoprotective when administered at 200 mg/kg [47]. A major limitation in human studies are high-doses administration, route of administration and bioavailability.

Ebselen

Ebselen is a potent glutathione peroxidase mimic and neuroprotectant. It also has strong activity against peroxynitrite, a super reactive oxygen species [48,49]. It reduces cytochrome c release from mitochondria and nuclear damage during lipid peroxidation [50]. Since it acts as a catalyst, low does maybe sufficient to prevent or treat noise induced hearing loss [51]. Phase II trials are currently in progress to determine the efficacy of oral ebselen.

Conclusion

Noise-induced hearing loss is a serious disease burden in the military. Due to the nature of the military profession, hearing is a vital asset during tactical and survival training and exposure to loud noises during training and missions are inevitable. Prevention is still the mainstay of treatment and soldiers need to be educated with regards to the use of hearing protection devices.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

JSY made significant contributions in preparing and writing the manuscript. DYW was substantially involved in writing and revising the manuscript for publication. Both authors have read and approved the final manuscipt. In

addition, both authors agree to be accountable for all aspects of the work. Both authors read and approved the final manuscript.

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Behavioral/Systems/Cognitive

Adding Insult to Injury: Cochlear Nerve Degeneration after "Temporary" Noise-Induced Hearing Loss

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Overexposure to intense sound can cause temporary or permanent hearing loss. Postexposure recovery of threshold sensitivity has been assumed to indicate reversal of damage to delicate mechano-sensory and neural structures of the inner ear and no persistent or delayed consequences for auditory function. Here, we show, using cochlear functional assays and confocal imaging of the inner ear in mouse, that acoustic overexposures causing moderate, but completely reversible, threshold elevation leave cochlear sensory cells intact, but cause acute loss of afferent nerve terminals and delayed degeneration of the cochlear nerve. Results suggest that noise-induced damage to the ear has progressive consequences that are considerably more widespread than are revealed by conventional threshold testing. This primary neurodegeneration should add to difficulties hearing in noisy environments, and could contribute to tinnitus, hyperacusis, and other perceptual anomalies commonly associated with inner ear damage.

Introduction

Noise-induced hearing loss (NIHL) is a major health problem (DHHS, 2009), because opportunities for overexposure abound, and exposures that damage hearing are not necessarily painful or even annoying. After overexposure, NIHL recovers with an exponential time course (Miller et al., 1963) for 2–3 weeks, depending on initial severity. Thresholds may fully recover ("temporary" threshold shift) or stabilize at an elevated value ("permanent" threshold shift). Permanent NIHL is due to destruction of cochlear hair cells or damage to their mechano-sensory hair bundles (Liberman and Dodds, 1984). Hair cells normally transduce sound-evoked mechanical motion into receptor potentials, which lead to transmitter release at their glutamatergic synapses with cochlear afferent fibers (see Fig. 1). Hair cell damage can be visible within minutes after overexposure, and hair cell death can continue for days (Wang et al., 2002). In contrast, noise-induced loss of spiral ganglion cells (SGCs), the cell bodies of the cochlear afferent neurons contacting these hair cells, is delayed by months and can progress for years (Kujawa and Liberman, 2006).

There is no hair cell death in temporary NIHL; however, swelling of cochlear nerve terminals at their hair-cell synapses, suggestive of glutamate excitotoxicity, is seen within 24 h after exposure (Spoendlin, 1971; Liberman and Mulroy, 1982; Robertson, 1983). Such sound-evoked excitotoxicity can be blocked by glutamate antagonists and mimicked by glutamate agonists in the absence of sound (Pujol et al., 1993; Sun et al., 2001; Puel et al., 2002; Ruel et al., 2007). Some noise or drug exposures can be followed by rapid postexposure recovery of cochlear synaptic ultrastructure and auditory thresholds, suggesting that swollen terminals have recovered or regenerated (Zheng et al., 1997; Puel et al., 1998; Zheng et al., 1999). Neuronal counts have not been made, however, and long survivals after apparently reversible noise exposures have not been evaluated.

Here, we revisit the issue of neural degeneration in ears with temporary noise-induced threshold shifts. We show rapid, extensive, and irreversible loss of synapses within 24 h postexposure, and delayed and progressive loss of cochlear neurons over many months, although hair cells remain and recover normal function. Despite recovery of threshold sensitivity, the consequences of such primary neuronal loss on auditory processing of suprathreshold sounds are likely dramatic, especially in difficult listening environments.

Materials and Methods

Animals and groups. Mice of the CBA/CaJ strain were used in this study, because they show excellent cochlear sensitivity and limited age-related elevation in cochlear thresholds. Male CBA/CaJ mice were noise exposed at 16 weeks of age and held without further treatment for various postexposure times. Age-, strain-, and gender-matched animals held identically, except for the exposure, served as controls. All procedures were approved by the Institutional Animal Care and Use Committee of the Massachusetts Eye and Ear Infirmary.

Acoustic overexposures. The acoustic overexposure stimulus was an octave band of noise (8–16 kHz) at 100 dB SPL, for 2 h. During exposures, animals were unrestrained within small cells in a subdivided cage (1 animal/cell). The cage was suspended directly below the horn of the sound-delivery loudspeaker in a small, reverberant chamber. Noise calibration to target SPL was performed immediately before each exposure session. Sound pressure levels varied by <1 dB across the cages.

Physiological tests. Mice were anesthetized with ketamine (100 mg/kg, i.p.) and xylazine (10 mg/kg, i.p.). Acoustic stimuli were delivered via a

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custom acoustic assembly consisting of two electrostatic drivers as sound sources (EC-1, Tucker Davis Technologies) and a miniature electret microphone at the end of a probe tube to measure sound pressure *in situ*. Auditory brainstem responses (ABRs) were recorded via subdermal needle electrodes (vertex–ventrolateral to pinna). For compound action potentials (CAPs) of the cochlear nerve, the recording electrode was placed at the round window niche. Stimuli were 5 ms tone pips with a 0.5 ms rise-fall time delivered at 30/s (ABR) or 16/s (CAP). The response from the electrodes was amplified, filtered, and averaged (512 samples, for ABR, or 128 samples, for CAP; polarity alternating). Sound level was incremented in 5 dB steps, from ~10 dB below threshold to 90 dB SPL. Threshold for ABR was defined as the lowest stimulus level at which a repeatable wave I could be identified in the response waveform. CAP threshold was defined as the sound pressure required to produce a wave I response of 6 μV peak to peak. For both neural responses, the wave I component was identified and the peak to peak amplitude computed by off-line analysis of stored waveforms. Distortion product otoacoustic emissions (DPOAEs) were recorded for primary tones with a frequency ratio of 1.2, and with the level of the f2 primary 10 dB less than f1 level, incremented together in 5 dB steps. Ear-canal sound pressure was amplified and digitally sampled, then fast Fourier transforms were computed and averaged by both waveform and spectral averaging. The 2f1-f2 DPOAE amplitude and surrounding noise floor were extracted. Iso-response contours were interpolated from plots of amplitude versus sound level. "Threshold" is defined as the f1 level required to produce a DPOAE of −5 dB SPL. To avoid distortion of nonphysiologic origin, stimulus levels were kept <80 dB SPL; in all cases, however, the range of noise-induced threshold shifts did not exceed the dynamic range available for response monitoring; i.e., there was no artificial "ceiling" limiting the measured threshold shifts. ABRs and DPOAEs were recorded from all animals, CAPs from subsets of animals just before tissue recovery for histological processing.

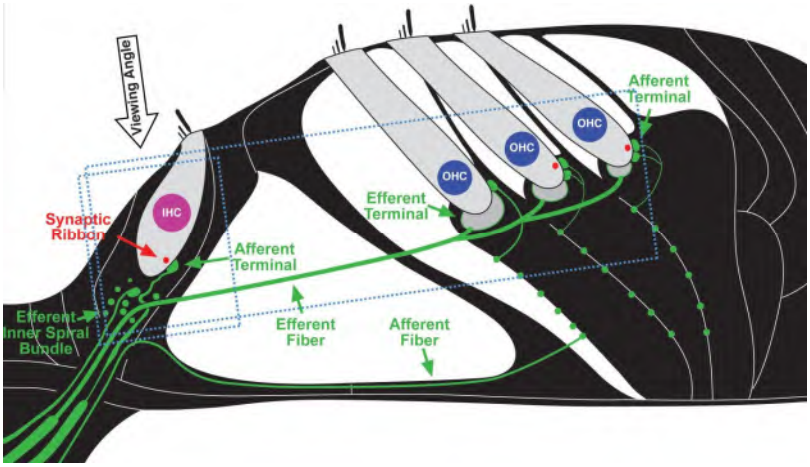

Figure 1. Schematic of the cochlear sensory epithelium showing inner and outer hair cells and their afferent innervation as they appear in tissue immunostained for neurofilament (green) and a synaptic ribbon protein (CTBP2: red). The approximate orientations of the confocal z stacks shown in subsequent figures are also indicated (small box for Figs. 4 and 8; larger box for Fig. 7): the viewing angle for the xy projections is noted. Efferent terminals in IHC and OHC areas have few neurofilaments and thus do not stain brightly in the confocal images.

Histologic preparation, confocal imaging and synaptic counts. For immunostaining and quantification of synaptic degeneration, cochleae were perfused with 4% paraformaldehyde and 0.25% glutaraldehyde, postfixed for 1–2 h, decalcified in EDTA, microdissected into 6 pieces and immunostained with antibodies to (1) C-terminal binding protein 2 (mouse anti-CtBP2 from BD Biosciences used at 1:200), and either (2) heavy neurofilaments (chicken anti-NF-H from Millipore Bioscience Research Reagents used at 1:1000), or (3) parvalbumin (goat anti-parvalbumin from Swant at 1:5000) and appropriate secondary antibodies coupled to Alexafluors in the red and green channels. A nuclear dye, TOPRO-3 was added to aid in hair cell counting, and in some cases, phalloidin (coupled to Alexafluor 568) was added to image stereocilia bundles. Immunostaining with postsynaptic markers such as glutamate receptors (rabbit anti-GluR2/3 from Millipore Bioscience Research Reagents) or proteins associated with the postsynaptic density (mouse anti-PSD-95 from Millipore Bioscience Research Reagents) did not survive the decalcification process required to reliably dissect entire cochleas from base to apex. Cochlear lengths were obtained for each case, and a cochlear frequency map computed to precisely localize inner hair cells (IHCs) from the 5.6, 8.0, 11.3, 22.6, 32, 45.2 and 64 kHz regions in each case. Confocal z-stacks of these 7 regions from each ear were obtained using a high-resolution [1.4 numerical aperture (N.A.)] oil-immersion objective and 2× digital zoom on a Leica TCS SP2. Care was taken to span the entire synaptic pole of the hair cells in the z-dimension, with a z-step-size of 0.25 mm, from the subjacent inner spiral bundle to the apical most ribbon or nerve terminal in the supranuclear region. Image stacks were ported to image-processing software (Amira: Visage Imaging), where synaptic ribbons were counted and divided by the total number of IHC nuclei in the microscopic field (including fractional estimates, when necessary, at the apical and basal ends of the image stack). To avoid underestimating ribbon counts due to superposition in the image stacks, three-dimensional (3-D) renderings were produced, using the "isosurface" feature in Amira, and rotated to disambiguate the xy projection images.

Histologic preparation and ganglion cell counts. For quantification of SGC death, animals were intravascularly perfused with a buffered solution of glutaraldehyde and paraformaldehyde. The temporal bones were removed, postfixed, osmicated, decalcified (0.1 M EDTA), dehydrated and embedded in Araldite in a strictly stereotyped orientation. Serial sections (40 μm thickness) were cut and mounted on microscope slides, and the precisely mid-modiolar section through the upper basal turn was identified: this area is known from 3-D reconstruction and cochlear mapping to correspond to the 32 kHz region. Using high-N.A. oil-immersion objectives and DIC optics, Rosenthal's canal in this cochlear region was live-imaged with a digital camera interfaced to Neurolucida software (MicroBrightField). Although the ganglion cell region appears darkly stained when viewed with low-power objectives, individual cells could be easily resolved with high-power objectives and high illumination levels (Supplemental Fig. 1, available at www.jneurosci.org as supplemental material). A mask corresponding to a rectangle 90 × 60 μm was superimposed on the image, and all ganglion cells with a nucleolus within that area (throughout the entire section thickness) were counted. Accuracy was insured by using the software to place a small marker at the xy position of each nucleolus, while repeatedly rolling the focus to image the entire depth of the section. To correct for possible variation in section thickness, the cell counts were divided by the true thickness of each section, as determined by imaging the top and bottom surface with DIC optics and reading output values of the calibrated *z*-axis sensor.

Results

In the mammalian inner ear (Fig. 1), the two classes of sensory cells have different roles: IHCs act as mechanoelectric transducers, releasing neurotransmitter to excite the sensory fibers of the cochlear nerve, whereas outer hair cells (OHCs) act as biological motors to amplify motion of the sensory epithelium. We use two complementary techniques for assessing cochlear function and the degree of noise-induced threshold shift in mice. When combined, they allow differential diagnosis of OHC versus IHC/neuro-

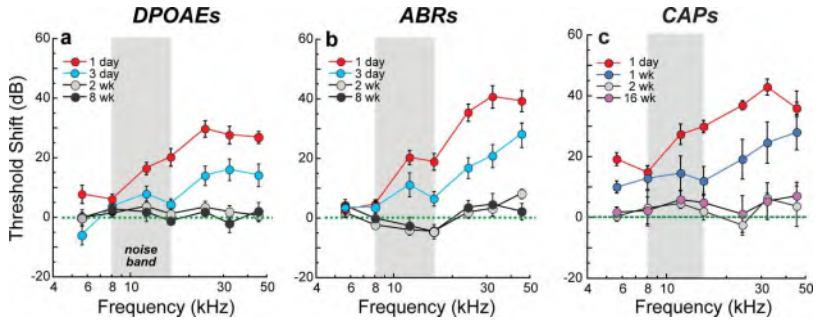

Figure 2. The level and duration of an acoustic overexposure were adjusted so that cochlear thresholds were elevated for several days before returning to normal. ***a–c***, A 2 h exposure to an octave-band (8–16 kHz) noise at 100 dB SPL produced ~40 dB maximum threshold shifts 1 d postexposure that recovered by 2 weeks to normal preexposure values, as assessed via DPOAEs (***a***), ABRs (***b***), and CAPs (***c***). Thresholds are expressed *re* age-matched unexposed controls. Group means ± SEMs are shown: $n = 6–21$ ears per group. ABR and DPOAE measurements are from the same animals; CAP thresholds are from a separate group.

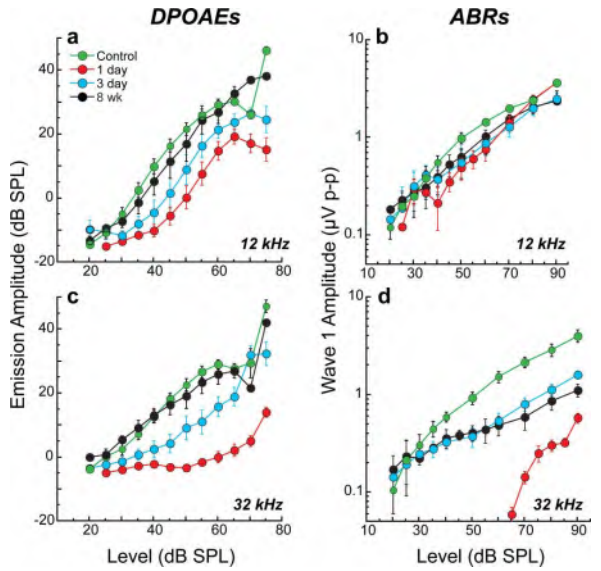

Figure 3. Despite threshold recovery, suprathreshold neural responses at high frequencies were permanently attenuated, although recovery of otoacoustic emissions suggests cochlear sensory cells are normal. ***b***, ***d***, At 8 weeks postexposure, suprathreshold amplitudes of ABR wave 1, the far-field response of the cochlear nerve, were less than half their preexposure values (***d***) in regions where temporary threshold shift was maximal (Fig. 2: 32 kHz), but recovered more completely (***b***) where initial shifts were less severe (Fig. 2: 12 kHz). ***a***, ***c***, In contrast, mean DPOAE amplitudes returned to normal by 8 weeks postexposure at both 12 kHz (***a***) and 32 kHz (***c***), suggesting complete recovery of OHC function, endolymphatic potentials, and cochlear mechanics. Together, these data suggest a primary loss of afferent innervation in the 32 kHz region. Group means ± SEMs are shown: $n = 7–21$ ears per group.

nal dysfunction throughout the cochlea, from the low-frequency apical turn to the high-frequency basal tip.

The auditory brainstem response (ABR) and the compound action potential (CAP), measured from scalp or round-window electrodes respectively, are sound-evoked potentials generated by neuronal circuits in the ascending auditory pathways: the first ABR or CAP wave represents summed activity of the cochlear nerve (Buchwald and Huang, 1975; Antoli-Candela and Kiang, 1978). ABRs can be recorded noninvasively at serial postexposure times. Although more invasive, the CAP potentials have a larger signal-to-noise ratio, and therefore can be a more sensitive indicator of subtle abnormalities.

To complement these measures of cochlear output, we assess OHC function via DPOAEs, which can be measured in the ear-canal sound pressure (Shera and Guinan, 1999). When two tones are presented to the normal ear, distortion components at additional frequencies are produced in the hair cell receptor potentials that can drive the OHCs' biological motors to move the sensory epithelium at the distortion frequencies. The resultant pressure waves from the motion of the epithelium are conducted back through the middle ear to the eardrum, which moves like a loudspeaker diaphragm to produce DPOAEs, which can be measured in the ear canal.

Noise-induced decrements in cochlear neural responses without changes in hair cell function

We adjusted the sound level and duration of an octave-band noise exposure to produce a moderate, but reversible, threshold elevation. At 24 h postexposure, this 2 h long, 100 dB SPL noise-band produced a 40 dB elevation of neural response thresholds (ABRs, CAPs) at high frequencies (Figs. 2*b*,*c*) coupled with slightly smaller threshold elevations in DPOAEs (Fig. 2*a*), suggesting substantial OHC dysfunction and an additional contribution of neural damage. Indeed, swelling of the peripheral terminals of cochlear nerve fibers in the IHC area is seen following these exposures (Wang et al., 2002). The upward spread of cochlear damage with respect to the exposure spectrum (Fig. 2) is typical of acoustic injury (Cody and Johnstone, 1981) and is well explained by level-dependent nonlinearities in cochlear mechanics (Robles and Ruggero, 2001). By 2 weeks postexposure, response thresholds returned to normal preexposure values and remained stable 8–16 weeks later (Fig. 2).

Although threshold sensitivity recovered, suprathreshold response decrements suggested loss of neurons in some cochlear regions (Fig. 3). At 32 kHz, where acute threshold shifts were large (Fig. 2), ABR amplitudes recovered to only ~40% of preexposure values (Fig. 3*d*), whereas at 12 kHz, where initial shifts were small, amplitude recovery was more complete (~80%) (Fig. 3*b*). In contrast, the amplitude-versus-level functions for the DPOAEs recovered completely at all test frequencies: mean data for 12 and 32 kHz are shown Figure 3, *a* and *c*, respectively. This neural response decrement coupled with full recovery of DPOAE amplitudes suggests neuronal loss in high-frequency regions, despite complete OHC recovery.

Noise-induced neural degeneration without loss of hair cells

Control ears

To quantify degeneration of cochlear hair cells and nerve terminals, and the synapses that connect them, we used confocal imaging of the sensory epithelium. As schematized in Figure 1, synapses were rendered visible by immunostaining for a component of the presynaptic "ribbon" (CtBP2), a structure characteristic of hair cell afferent synapses and likely involved in vesicle delivery to the active zone (Khimich et al., 2005). To assess cochlear nerve terminals, we used either anti-neurofilament immunostaining (Figs. 4, 5), to reveal all the unmyelinated nerve fibers in the sensory epithelium, or anti-parvalbumin (a calcium buffer), which stains only the terminal swellings of cochlear nerve

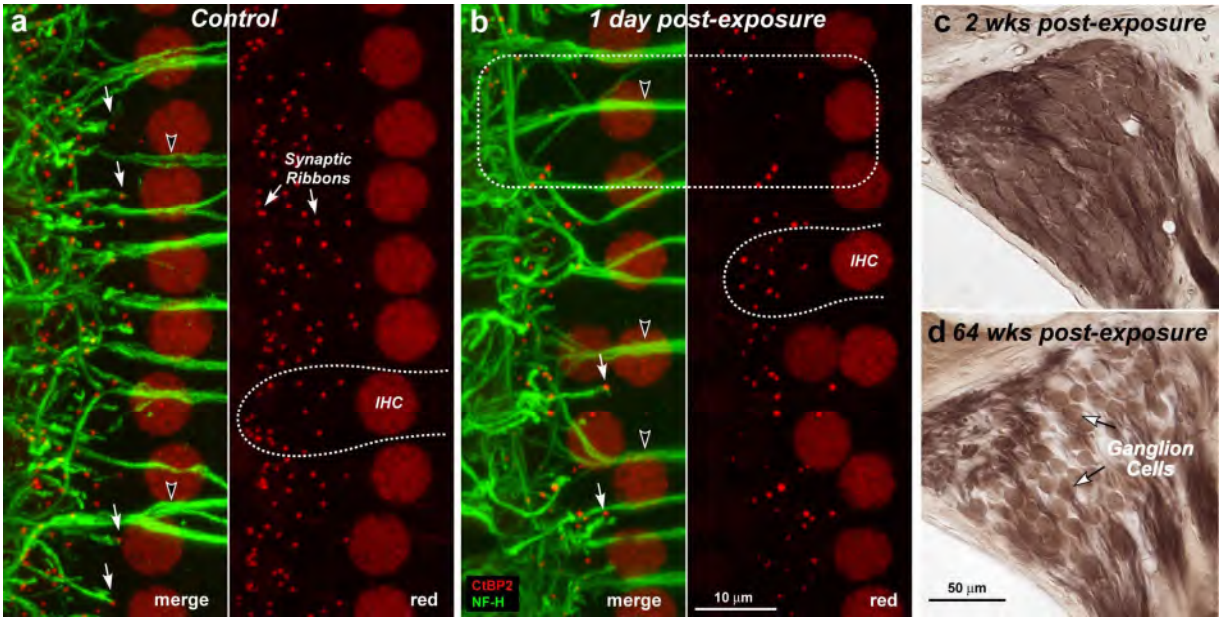

Figure 4. ***a–d***, Despite reversibility of threshold shift and intact sensory cells, noise-exposed ears show rapid loss of cochlear synaptic terminals (***a***, ***b***) and delayed loss of cochlear ganglion cells (***c***, ***d***). Immunostaining reveals synaptic ribbons (red, anti-CtBP2) and cochlear nerve dendrites (green, anti-neurofilament) in the IHC area of a control (***a***) and an exposed (***b***) ear at 1 d post noise. Outlines of selected IHCs are indicated (***a***, ***b***: dashed lines); the position of IHC nuclei is more irregular in the traumatized ears. Each confocal image (***a***, ***b***) is the maximum projection of a z-series spanning the IHC synaptic region in the 32 kHz region: the viewing angle is from the epithelial surface (see Fig. 1). Each image pair (red/merge) shows the same confocal projection without, or with, the green channel, respectively. Merged images show juxtaposed presynaptic ribbons and postsynaptic terminals, in both control and exposed ears (***a***, ***b***: filled arrows), and the lack of both in denervated regions (***b***: dashed box). Anti-CtBP2 also stains IHC nuclei; anti-neurofilament also stains efferent axons to OHCs (***a***, ***b***: unfilled arrowheads). Cochlear sections show normal density of ganglion cells 2 weeks postexposure (***c***) compared with diffuse loss after 64 weeks (***d***): both images are from the 32 kHz region of the cochlea.

fibers under the IHCs (Fig. 6). Antibodies to the postsynaptic glutamate receptors (AMPA-type) that are present in cochlear nerve terminals (Matsubara et al., 1996) work well only in lightly fixed and undecalcified tissue, from which it is impossible to dissect the basal half of the cochlea, where the major noise-induced damage is seen.

In the mammalian cochlea, outside of the extreme apex, >95% of cochlear nerve fibers are unbranched, contacting a single IHC via a single terminal swelling (Fig. 1), with a single active zone at which a single presynaptic ribbon is tethered to the IHC membrane (Liberman et al., 1990). Thus, ribbon counts in normal ears provide an accurate metric of the IHC afferent innervation. In 11 control ears, we used confocal z-stacks (Fig. 4*a*) to count synaptic ribbons in five cochlear regions (from apex to base), converting cochlear location to cochlear frequency according to the map for the mouse (Taberner and Liberman, 2005). Mean counts in control ears showed a broad peak of ~17 ribbons/IHC in mid-cochlear regions, declining to ~10 ribbons/IHC toward the apical and basal ends (Fig. 7). These values closely match electron-microscopic counts of afferent synapses

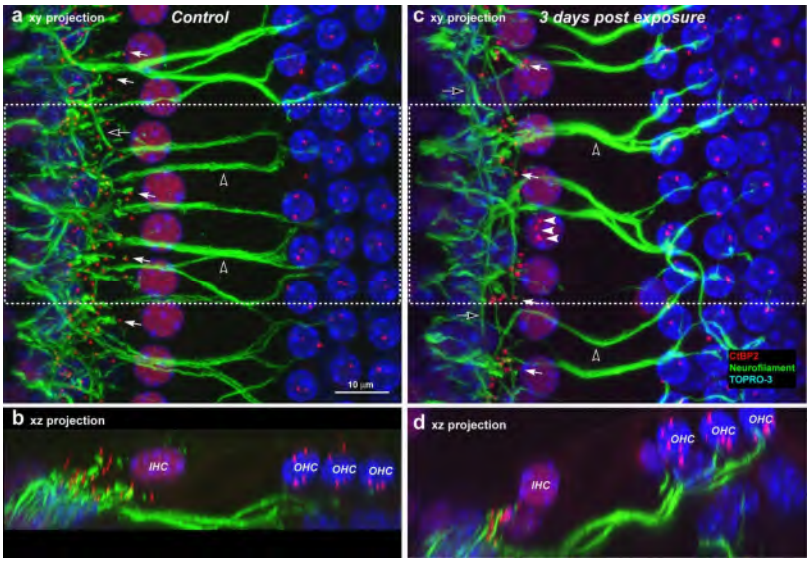

Figure 5. Double-staining for anti-neurofilament (green) and anti-CtBP2 (red) suggests cochlear nerve terminals have disappeared where there is loss of synaptic ribbons. ***a–d***, Tissues double stained for anti-neurofilament (green) and anti-CtBP2 (red) are shown as confocal projections of the 45 kHz region from a control (***a***, ***b***) and an exposed (***c***, ***d***) ear 3 d after noise; viewed from the surface of the sensory epithelium (xy projections in ***a***, ***c***) and in cross-section views (xz projection, ***b***, ***d***) of half the extent in the *x* dimension (dashed box). The dramatic reduction in cochlear terminals is especially clear in the xz projections. In the xy projections, filled arrows indicate some of the synaptic ribbons paired with nerve terminals; filled arrows (***c***) point to three ribbons that are displaced from the basolateral IHC membrane and appear uncoupled from nerve terminals. Open arrows (***a***, ***c***) point to spiraling efferent axons in the inner spiral bundle and the open arrowheads show efferents to OHCs crossing the tunnel of Corti. Scale bar in ***a*** applies to all panels.

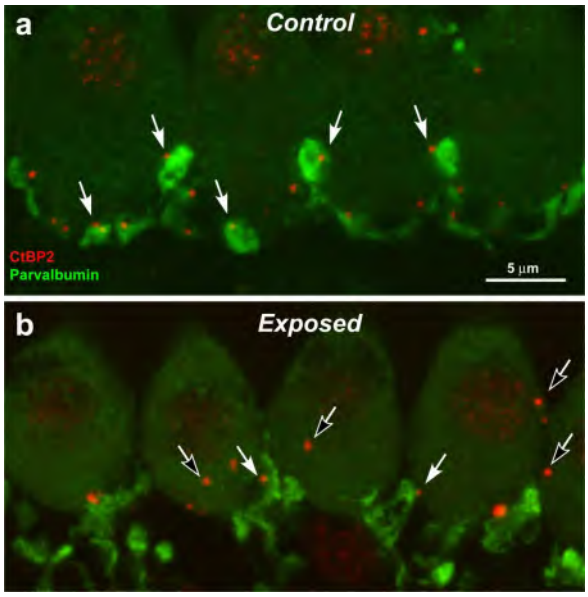

Figure 6. Immunostaining cochlear-nerve terminal swellings suggests that ribbon counts underestimate the degree of IHC denervation. ***a***, ***b***, These confocal projections of the IHC area in the 45 kHz region of a control ear (***a***) and an ear 3 d postexposure (***b***) are immunostained with anti-parvalbumin (green), which stains terminal swellings, and anti-CtBP2 (red), which stains synaptic ribbons. In the control ear, there is close to a one-for-one relation between ribbons and terminals (e.g., filled arrows). In the exposed ear, almost all terminals are near a ribbon (e.g., filled arrows); however, some ribbons are not paired with terminals (e.g., unfilled arrows): some appear intracellular, i.e., far from the IHC membrane. The vacuolization of terminals in the exposed ear is part of the acute excitotoxic response to overstimulation (Wang et al., 2002).

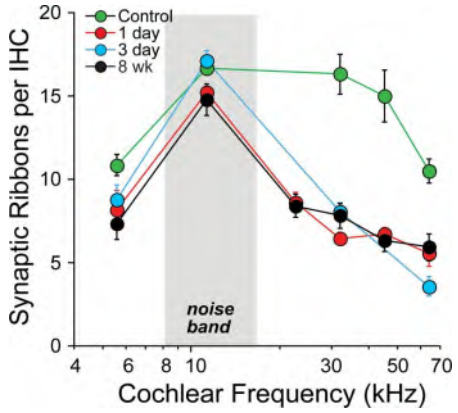

Figure 7. Synaptic ribbon counts in six cochlear regions of control and noise-exposed ears show synaptic loss throughout the basal half of the cochlea. Mean numbers (±SEMs) of synaptic ribbons per IHC were computed from confocal z-stacks such as those in Figure 2 from control ears ($n = 11$) and exposed ears at 6 cochlear locations and 4 postexposure times: 1 d ($n = 6$), 3 d ($n = 5$), and 8 weeks ($n = 6$).

(mean = 16.8/IHC) from serial sections of IHCs in mid-cochlear regions of the mouse (Stamataki et al., 2006) and ribbon counts versus cochlear place determined by confocal microscopy (Meyer et al., 2009).

The neurofilament/CtBP2 double-immunostain reveals the normal relation between cochlear nerve terminals and hair cell synaptic ribbons. In the control ear, almost all IHC ribbons are coupled with a nerve terminal, if they are sufficiently isolated to be resolvable (Figs. 4*a* and 5*a*, filled arrows). Since neurofilaments do not fill the terminal swellings, we also used antibodies against parvalbumin (Fig. 6*a*), which does fill them. The parvalbumin immunostaining reveals a one-for-one relation between terminal swellings and ribbons in the control ear (for some ribbons, the associated terminals are in deeper focal planes). These light-microscopic observations of a one-for-one coupling between ribbons and terminals are consistent with conclusions from serial section ultrastructural studies in both cat (Liberman, 1980b) and mouse (Stamataki et al., 2006).

Noise-exposed ears

In noise-exposed ears, there was no loss of hair cells, either IHCs or OHCs, at any postexposure time out to at least 1 year. Images from 1 and 3 d postexposure show the normal array of nuclei in both IHC and OHC areas: since anti-CtBP2 also stains IHC nuclei, they appear red in Figure 4; when a fluorescent nuclear stain is added (blue channel: TOPRO-3), IHC nuclei appear purple, and the three rows of OHC nuclei are blue (Fig. 5). Stereocilia bundles appeared normal at the light microscopic level, even at 24 h postexposure (Supplemental Fig. 2, available at www.jneurosci.org as supplemental material), when the temporary threshold shifts were 20–40 dB (Fig. 2).

Despite the normal hair cell populations, there was dramatic degeneration of both presynaptic and postsynaptic elements in the IHC area throughout the high-frequency (basal) half of the cochlea. This degeneration was observed at all postexposure times, beginning at 24 h, the earliest time examined. Presynaptic ribbons were decreased in number, many remaining ribbons were abnormally large, and some ribbons were displaced away from the basolateral IHC membrane toward the cell nucleus (Figs. 4*b*, 5*c*). Ribbons were counted in at least five cochlear regions from noise-exposed ears at three postexposure times from 1 d to 8 weeks (Fig. 7). In the 32 kHz region of noise-exposed ears, where acute threshold shifts were greatest (Fig. 2) and where persistent ABR amplitude decrements suggested significant neuronal loss (Fig. 3*d*), ribbon counts were reduced from ~16 to <7/IHC at 24 h postexposure. Numbers had not recovered 8 weeks later. In contrast, in the 12 kHz region, where initial threshold shifts were small (Fig. 2), and amplitude recovery was essentially complete (Fig. 3*b*), decreases in ribbon number in the noise-exposed ears were correspondingly small (Fig. 7). Ribbons in the OHC area appeared unchanged in number and morphology in all cochlear regions at all survival times (Fig. 5*a*,*c*).

In noise-exposed ears, fiber density in the IHC area was reduced, at all postexposure times, in proportion to the loss of ribbons. Although the terminal plexus under each IHC is too complicated to allow fiber counts or other quantitative measures, the decreased density of neurofilament-positive elements is obvious to qualitative assessment (Figs. 4*b*, 5*c*). The proportional loss of ribbons and terminals is particularly clear in xy projections in regions where ribbon counts are especially reduced (Fig. 4*b*, e.g., dashed box) and in the xz projections where the organ of Corti is viewed in cross-section (Figs. 5*b*,*d*). Note that many of the remaining neurofilament-positive elements in the noise-exposed ears are efferent fibers from the olivocochlear bundle (Fig. 1), which appear unaffected: the thick fibers crossing the tunnel of Corti (Figs. 4 and 5, open arrowheads) are medial olivocochlear neurons projecting to OHCs (Spoendlin and Gacek, 1963), and the thin fibers spiraling under the IHCs (Fig. 5, unfilled arrows) are lateral olivocochlear fibers in the inner spiral bundle targeting cochlear nerve dendrites (Liberman, 1980a).

The ribbon counts in noise-exposed ears may underestimate the neural degeneration, because many ribbons included in these counts are far from the basolateral membrane (Fig. 5*c*, filled ar-

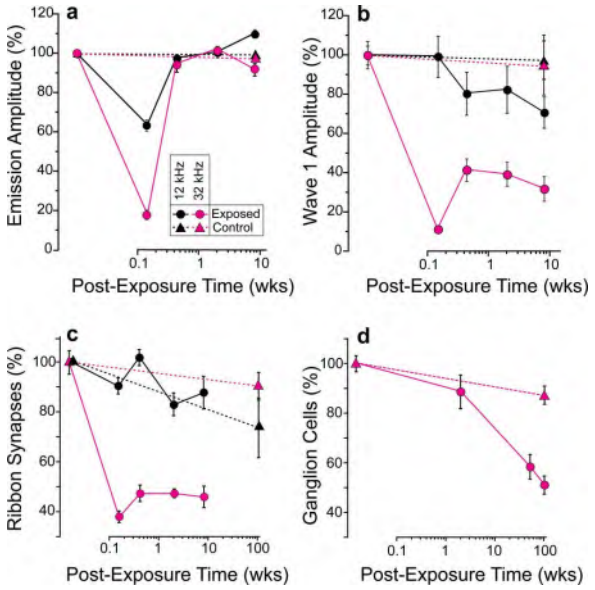

Figure 8. ***a–d***, Normalized functional and histopathological metrics versus postexposure time show a close match between synaptic loss (***c***) and loss of neural amplitudes (***b***); ganglion cell loss (***d***) is significantly delayed and hair cell responses (***a***) return to normal. There is a close match between synaptic loss (***c***) and loss of neural amplitudes (***b***); ganglion cell loss (***d***) is significantly delayed and hair cell responses (***a***) return to normal. Suprathreshold response amplitudes (***a***, ***b***) are for 80 dB SPL; complete growth functions are in Figure 3. Values are expressed as a percentage of control means (± SEMs, $n = 7$–21 per group). Loss of ribbons was quantified (***c***) by comparing age-matched controls ($n = 11$) to exposed ears at four postexposure times: 1 d ($n = 6$), 3 d ($n = 5$), 2 weeks ($n = 4$), and 8 weeks ($n = 6$). Data from two cochlear regions are shown: 12 kHz and 32 kHz (see key). To control for aging, ribbons were counted in unexposed 104 week animals ($n = 3$: triangles in ***c***). Loss of ganglion cells (***d***) was quantified at the 32 kHz place in control ($n = 7$) and exposed ears at 3 postexposure times: 2 weeks ($n = 6$), 52–64 weeks ($n = 7$) and 104 weeks ($n = 6$). To control for aging, cells were counted in unexposed 104 week animals ($n = 12$: triangles in ***e***). For all counts (***c***, ***d***), means ± SEMs are shown, and data are expressed as a percentage of values from unexposed 16 week animals.

rowheads) and thus not at active zones where terminals are present. The parvalbumin staining shows that, in exposed ears, some of the ribbons we count lack apposed terminals (Fig. 6*b*, open arrows), yet very few terminal swellings lack apposed ribbons. Such an underestimation is supported by the quantitative comparisons between neural response decrements and ribbon losses summarized in Figure 8: 8 weeks postexposure, neural amplitudes were decreased by >60% at 32 kHz, whereas ribbon counts were decreased by ~50%; at 12 kHz, response amplitudes were reduced by ~30%, whereas ribbon counts were decreased by ~10%. Similar results were seen in the cochlear nerve CAPs, where amplitudes remained depressed by >60% out to at least 64 weeks postexposure (data not shown). In contrast, OHC-based DPOAE amplitudes (Fig. 8*a*) returned to normal values within days of exposure and remained stable over the period of postexposure monitoring.

Although the loss of peripheral terminals of the cochlear neurons was rapid, the death of the cell and the disappearance of the somata were extremely slow. To evaluate this delayed neural degeneration, we counted SGCs in tissue sections (Supplemental Fig. 1, available at www.jneurosci.org as supplemental material) from separate groups of noise-exposed animals. As quantified in Figure 8*d*, ganglion cell numbers in the 32 kHz region were close to normal at 2 weeks postexposure. However, by ~1 year, dramatic loss was seen throughout the basal turn in every ear (Figs. 4*d*, 8*d*), and by 2 years, cell counts near the 32 kHz region had decreased by ~50% (Fig. 8*d*), comparable to ribbon losses seen in the first 24 h after exposure (Figs. 7, 8*c*). Hair cell populations remained intact in corresponding regions. Ganglion cell loss was modest (<10%) in unexposed, aging animals (Fig. 8*d*, triangles), mirrored by similarly modest age-related decreases in both IHC ribbon counts (Fig. 8*c*, triangles) and suprathreshold neural responses (data not shown).

Discussion

Threshold recovery despite neuronal loss: resolving the paradox

The rapid postexposure loss of presynaptic ribbons and postsynaptic terminals documented here must functionally silence the affected neurons, despite complete recovery of hair cell function. Such a conclusion is supported by the parity (Fig. 8) between the degree of ribbon loss and the fractional decrement in neural response amplitudes in the affected high-frequency cochlear regions. Such neurodegeneration is not inconsistent with the observed recovery of threshold sensitivity. Thresholds for sound-evoked neural potentials are insensitive to diffuse neuronal loss (Liberman et al., 1997; El-Badry and McFadden, 2007), so long as hair cells, particularly OHCs, are functioning normally. Behavioral thresholds also are unaffected by diffuse neuronal loss, as seen in a study of trained cats before and after partial section of the cochlear nerve (Schuknecht and Woellner, 1953).

To understand why neural degeneration is reflected in neural response amplitudes (Fig. 3*d*), but not thresholds (Fig. 2), consider that threshold is defined by a criterion response amplitude, just above the measurement noise floor (~0.1 μV for mouse ABRs: Fig. 3*b*,*d*). With a criterion of 0.25 μV, thresholds are increased by <5 dB at 8 weeks postexposure (Fig. 3*d*), although amplitudes are reduced by >50%. Consider also that ABR amplitude is a function of both the sound-evoked discharge probability of each responding fiber and the number of fibers responding synchronously (Kiang et al., 1976). Thus, diffuse loss of half the cochlear nerve and the resultant 50% decrease in response amplitude, can be compensated either by doubling the discharge rates in remaining neurons or doubling the number of neurons responding. Either of these compensatory increases is accomplished with only a few dB increase in stimulus level, because, discharge rate in cochlear neurons climbs steeply near threshold, and activity spreads quickly to neurons with higher or lower best frequencies (Taberner and Liberman, 2005).

Although DPOAE and ABR thresholds are sensitive metrics of hair cell damage, they are quite insensitive to "primary" neuronal degeneration, i.e., loss of cochlear neurons without loss of hair cells. Practically, using threshold as a high-throughput screening tool for deafness phenotype, e.g., in mutagenesis studies (Kermany et al., 2006), selects against discovery of primary neuronal disorders, thereby reinforcing the sense that such disorders are rare, compared to the "secondary" neuronal degeneration seen weeks and months after IHC death. Behavioral thresholds, too, can fail to provide evidence of underlying neurodegeneration (Schuknecht and Woellner, 1953). Thus, dependence on this measure, alone, to quantify noise-induced damage in humans is seriously flawed.

Primary versus secondary degeneration: how primary loss has gone unnoticed

After high-level noise exposure, hair cell loss can be seen in minutes to hours, whereas SGC loss is not seen for weeks to months

(Spoendlin, 1971; Johnsson, 1974; Lawner et al., 1997). This difference in degenerative time course, and the correlation, in long-surviving ears, between regions of hair cell loss (particularly IHCs) and regions of SGC death (Liberman and Kiang, 1978), has suggested that hair cells are the primary targets of acoustic overexposure, whereas noise-induced SGC death occurs only as a secondary event to the loss of hair cells and, perhaps, of the neurotrophins they provide (Glueckert et al., 2008).

In contrast, the present results show that noise-induced SGC death can be extensive despite a normal hair cell complement. Prior evidence for direct noise-induced neuronal damage has not been lacking. Swelling of cochlear nerve terminals is seen in the IHC area 24–48 h after overexposure, even when threshold shifts are ultimately reversible (Liberman and Mulroy, 1982; Robertson, 1983). The same acute swelling is observed after cochlear perfusion of glutamate agonists, and the same recovery of cochlear neural thresholds has been noted (Zheng et al., 1997, 1999). Based on the lack of swollen terminals at longer survivals, the recovery of threshold sensitivity, and the occasional presence of growth-cones in damaged ears (Puel et al., 1998), previous studies have suggested that noise- or drug-damaged terminals either recover or regenerate (Pujol et al., 1993; Zheng et al., 1997; Puel et al., 1998; Pujol and Puel, 1999; Zheng et al., 1999; Ruel et al., 2007). However, neuronal counts were not made, and ears were not followed for extended postexposure times.

The present quantitative analysis of hair cell synapses, cochlear nerve terminals and SGCs suggests a different view, i.e., that the acute noise-induced damage to cochlear nerve terminals is irreversible in the adult, and that there is minimal nerve regeneration or renewed synaptogenesis after noise. Significant terminal regrowth and reconnection can be seen in neonatal cochleas *in vitro* after chemically mediated neurodegeneration (Brugeaud and Edge, 2009). In the adult ear, however, the close agreement between the acute loss of synapses/terminals and the delayed loss of cell bodies suggests that the long-term fate of SGCs is sealed within the first 24 h postexposure, although it may take years for the cells to degenerate. We previously observed a slow-onset loss of SGCs in exposed ears with damaged, but surviving, hair cells and a corresponding permanent noise-induced hearing loss of ~40 dB (Kujawa and Liberman, 2006). Lacking knowledge of the rapid synaptic changes revealed here, we viewed this slow neurodegeneration as an age/noise interaction of indeterminate origin. Confocal analysis has since revealed a similar degree of acute synaptic degeneration (data not shown), suggesting that, whether or not surviving hair cells recover, noise-induced slow-onset primary neural degeneration may always be preceded by rapid loss of synaptic terminals.

Together, these observations suggest that much noise-induced degeneration of the cochlear nerve is primary, in that it will occur in the absence of hair cell damage. Such primary neural loss may never exceed 50–60% (the most we have observed), thus the less vulnerable 40–50% may die only secondarily to loss of hair cells or supporting cells in the organ of Corti.

Mechanisms of rapid synaptic loss versus slow neuronal death

The immunostaining patterns in our noise-exposed ears suggest that, within hours after an exposure at the limits of threshold-shift reversibility, roughly half the presynaptic ribbons disappear from IHCs, along with a corresponding proportion of the (unmyelinated) postsynaptic afferent terminals that formerly contacted them. At this early postexposure time, there is no obvious loss of myelinated peripheral axons. Thus, the terminal retraction apparently proceeds only as far centrally as the first node of Ranvier, where it pauses, before continuing in a second wave of degeneration in which the peripheral axon disappears (Liberman and Kiang, 1978). Several observations suggest that this terminal damage arises from a type of excitotoxicity involving AMPA receptors at these glutamatergic afferent synapses: (1) the phenomenon can be mimicked by cochlear perfusion of exogenous glutamate receptor agonists such as AMPA and kainate (Pujol et al., 1993), (2) it can be blocked by antagonists of AMPA receptor-mediated transmission (Ruel et al., 2000); and (3) it is not seen in the OHC area (Robertson, 1983), where, correspondingly, AMPA receptors are not expressed (Matsubara et al., 1996).

Once the terminal has retracted, the slow-onset degeneration of the cell body and axons may result from withdrawal of the neurotrophin signaling among hair cells, supporting cells and nerve terminals. In the cochlea, the key neurotrophin, NT-3, is expressed by IHCs and their support cells in response to neuregulin released by the neurons. Blockade of this signaling pathway, by dominant-negative neuregulin receptors in supporting cells leads to primary neuronal degeneration (Stankovic et al., 2004). Retraction of peripheral terminals after noise damage may suppress the neurotrophin cascade by increasing the distance between the ligand release sites and their respective receptors on neurons and epithelial cells in the organ of Corti. The reasons for the extremely slow time course remain unclear.

Relevance to sensorineural hearing loss in humans

The primary neural degeneration described here likely occurs in noise-exposed human ears as well: (1) acute noise-induced swelling of cochlear-nerve terminals has been observed in every mammal studied, including cat (Liberman and Mulroy, 1982), guinea pig (Robertson, 1983; Pujol et al., 1993) and mouse (Wang et al., 2002); (2) the mouse strain we use (CBA/CaJ) has noise vulnerability typical of other mammals (Yoshida et al., 2000); and (3) the same synaptic loss without hair cell damage is seen in guinea pigs after an exposure at the limit of threshold reversibility (data not shown). Indeed, human SGC counts decline dramatically with age (Otte et al., 1978) and can be seen in areas remote from regions of threshold elevation (Felder and Schrott-Fischer, 1995). Since IHC sensory fibers constitute 95% of the cochlear nerve (Spoendlin, 1972), dysfunction in this neural population must have important consequences for hearing, even if threshold sensitivity recovers. Loss of cochlear neurons should decrease the robustness of stimulus coding in low signal-to-noise conditions, for example speech in noise, where spatial summation via convergence of activity from groups of neurons must be important in signal processing. Peripheral neurodegeneration also can lead to changes in brainstem circuitry and cortical reorganization, with overrepresentation of surviving cochlear regions (Irvine et al., 2000). These changes may contribute to other postexposure perceptual anomalies, including tinnitus (perception of phantom sounds) and hyperacusis (intolerance of moderately intense stimuli), classic sequelae of sound overexposure that can occur with or without threshold elevation (Bauer et al., 2007; Eggermont, 2007).

It is sobering to consider that normal threshold sensitivity can mask ongoing and dramatic neural degeneration in noise-exposed ears, yet threshold sensitivity represents the gold standard for quantifying noise damage in humans. Federal exposure guidelines (OSHA, 1974; NIOSH, 1998) aim to protect against

permanent threshold shifts, an approach that assumes that reversible threshold shifts are associated with benign levels of exposure. Moreover, lack of delayed threshold shifts after noise has been taken as evidence that delayed effects of noise do not occur (Humes et al., 2005). The present results contradict these fundamental assumptions by showing that reversibility of noise-induced threshold shifts masks progressive underlying neuropathology that likely has profound long-term consequences on auditory processing. The clear conclusion is that noise exposure is more dangerous than has been assumed.

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REVIEW

Noise-induced and age-related hearing loss: new perspectives and potential therapies

[version 1; peer review: 4 approved]

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Abstract

The classic view of sensorineural hearing loss has been that the primary damage targets are hair cells and that auditory nerve loss is typically secondary to hair cell degeneration. Recent work has challenged that view. In noise-induced hearing loss, exposures causing only reversible threshold shifts (and no hair cell loss) nevertheless cause permanent loss of >50% of the synaptic connections between hair cells and the auditory nerve. Similarly, in age-related hearing loss, degeneration of cochlear synapses precedes both hair cell loss and threshold elevation. This primary neural degeneration has remained a "hidden hearing loss" for two reasons: 1) the neuronal cell bodies survive for years despite loss of synaptic connection with hair cells, and 2) the degeneration is selective for auditory nerve fibers with high thresholds. Although not required for threshold detection when quiet, these high-threshold fibers are critical for hearing in noisy environments. Research suggests that primary neural degeneration is an important contributor to the perceptual handicap in sensorineural hearing loss, and it may be key to the generation of tinnitus and other associated perceptual anomalies. In cases where the hair cells survive, neurotrophin therapies can elicit neurite outgrowth from surviving auditory neurons and re-establishment of their peripheral synapses; thus, treatments may be on the horizon.

Keywords

sensorineural hearing loss, noise-induced hearing loss, auditory neurons,

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Introduction

According to the Centers for Disease Control, 25% of American adults suffer from some form of noise-induced hearing loss (NIHL). Our ears were not designed to withstand long and repeated exposure to the high sound pressures produced by the machinery that surrounds us in modern industrialized society, be it work-, leisure- or combat-related. Correspondingly, with increasing life expectancy, the prevalence of age-related hearing loss (AHL) is also on the rise. The National Institute on Deafness estimates that 33% of people over the age of 65 have significant hearing impairment. The two types of hearing loss are likely interrelated, as people in minimally industrialized areas (e.g. the Sudanese desert) do not show the inexorable age-related deterioration of hearing seen in the developed world[1].

Both NIHL and AHL are known as sensorineural hearing loss because the dysfunction arises in the inner ear, or cochlea, where sound-induced vibrations are transduced by sensory hair cells into electrical signals in cochlear neurons that relay the encoded information to the brain (Figure 1). For decades, we've known that hair cell damage is a key contributor to the hearing loss in NIHL and AHL[2–4], as defined by the audiogram, which measures the minimal sound pressure required for pure-tone detection in a quiet test booth. For decades, it was assumed that cochlear neural loss occurred only after hair cell death[5] and thus was rarely of functional significance in NIHL or AHL.

Recently, my lab showed, in both NIHL and AHL, that synaptic connections between hair cells and cochlear neurons can be destroyed well before the hair cells are damaged[6]. This synaptic loss silences large numbers of cochlear neurons but is invisible in routine histological material and does not affect tests of threshold detection, so long as the loss is not complete. This cochlear synaptopathy, also known as "hidden hearing loss", compromises performance on difficult listening tasks such as understanding speech in a noisy environment, which is the classic complaint of those with NIHL and AHL. In animal models, post-exposure treatment with neurotrophins, delivered locally to the inner ear, can repair or replace the damaged synapses[7], suggesting possible future therapies for some of the most disabling sensory impairments in sensorineural hearing loss.

Normal cochlear function

The mammalian cochlea is a spiraling, fluid-filled tube within a particularly dense bone (Figure 1a). In cross-section, the spiraling bony tube is bisected by a membranous tube called the cochlear duct, the lumen of which is lined with epithelial cells, including three rows of outer hair cells (OHCs) and one row of inner hair cells (IHCs) (Figure 2a). Each hair cell has, at its lumenal end, a "hair bundle", i.e. a tuft of modified microvilli, called stereocilia, where the mechanoelectrical transduction channels are found. Sound-evoked vibration of the sensory epithelium opens these channels, causing hair cell depolarization and release of neurotransmitter (glutamate) from the other end of the hair cell, where synapses with auditory nerve fibers (ANFs) are located (Figure 2b). The entire spiraling sensory epithelium is mechanically tuned and is most responsive to high frequencies at the "basal" end, i.e. closer to the stapes, and to low frequencies at the "apical" end (Figure 1b and c).

In humans, the cochlear spiral is ~32 mm long and contains roughly 3,200 IHCs and 10,000 OHCs[8]. The two hair cell types have different functions. The OHCs have been called the "cochlear amplifier" because they possess electromotility, which is

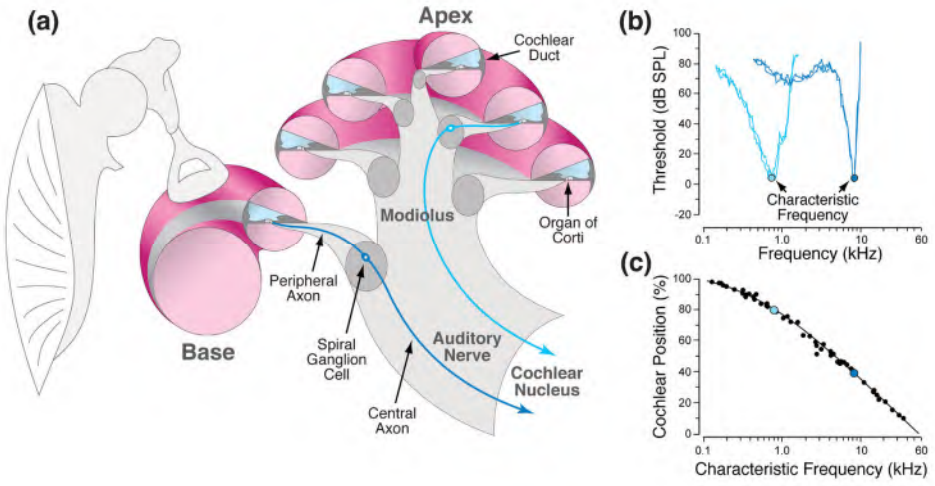

Figure 1. Mapping of characteristic frequency along the cochlear spiral. (**a**) Schematic showing middle ear bones and a cross-section through the cochlear spiral, illustrating perilymph (pink) and endolymph spaces (blue) and two auditory nerve fibers (ANFs), one high-frequency (deep blue) and one low-frequency (cyan), traveling from organ of Corti through the modiolus to the cochlear nucleus. (**b**) Tuning curves for a high- and a low-frequency ANF, showing threshold as a function of frequency. The characteristic frequency[48] defines where the fiber originates along the mechanically tuned cochlear spiral. (**c**) Cochlear frequency map derived from intracellular labeling in the cat defines the precise relationship between characteristic frequency and cochlear location[76]. dB SPL, decibels sound pressure level.

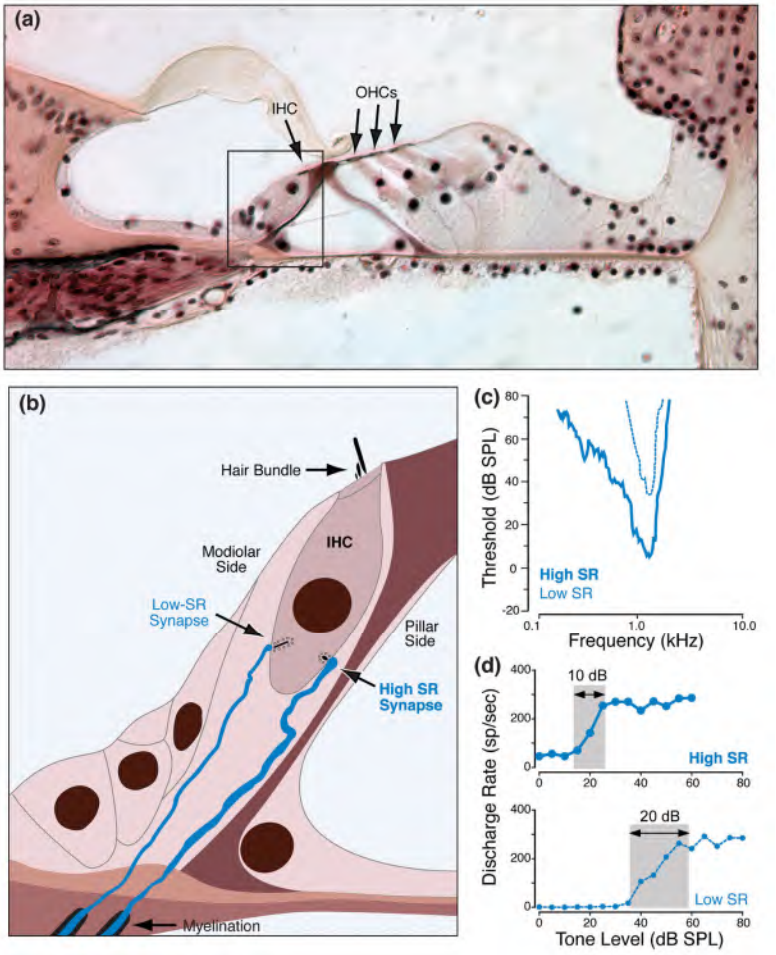

Figure 2. High- vs. low-SR auditory nerve fibers and their synaptic localization on the inner hair cell. (**a**) Light micrograph of the organ of Corti, as it appears in conventional histological material, stained with hematoxylin and eosin. Peripheral terminals of auditory nerve fibers (ANFs) in the inner hair cell (IHC) area (box) are not resolvable. (**b**) Schematic of type I peripheral terminals showing that fibers with high versus low spontaneous discharge rates (SRs) make synaptic contacts on opposite sides of the IHC. (**c**) High-SR fibers have lower thresholds than do low-SR fibers, as shown by these two tuning curves. (**d**) High-SR fibers have smaller dynamic ranges (grey box) than do low-SR fibers when stimulated with tone bursts at the characteristic frequency. dB SPL, decibels sound pressure level; OHC, outer hair cell.

driven by molecular motors containing a membrane protein called prestin[9]. Prestin undergoes a voltage-sensitive conformational change that turns sound-driven hair-cell receptor potentials back into mechanical motion that is powerful enough to vibrate the entire sensory epithelium, including the IHC stereocilia. The IHCs are more conventional sensory receptors, generating the presynaptic drive for all the myelinated sensory fibers of the auditory nerve. Each ANF has a bipolar "type I" cell body in the spiral ganglion that sends a myelinated peripheral axon towards the sensory epithelium, where its unmyelinated terminal contacts a single IHC, and a myelinated central axon to the cochlear nucleus (Figure 3), the first central processing station in the ascending auditory pathway[10]. In humans, as shown in Figure 4, each IHC is contacted by 4–13 ANFs[11,12] depending on cochlear location; thus, each auditory nerve contains ~40,000 myelinated sensory fibers. The OHCs are contacted by a much smaller population (5–10%) of thin, unmyelinated fibers[13]. These "type II" ANFs also project to the cochlear nucleus[14]. Their function is unclear, but they may be nociceptors[15–17].

Hearing loss and hair cell damage in AHL and NIHL

As for most types of hearing dysfunction, characterizing NIHL and AHL in humans begins with the threshold audiogram, which measures the lowest audible sound pressure for pure tones at

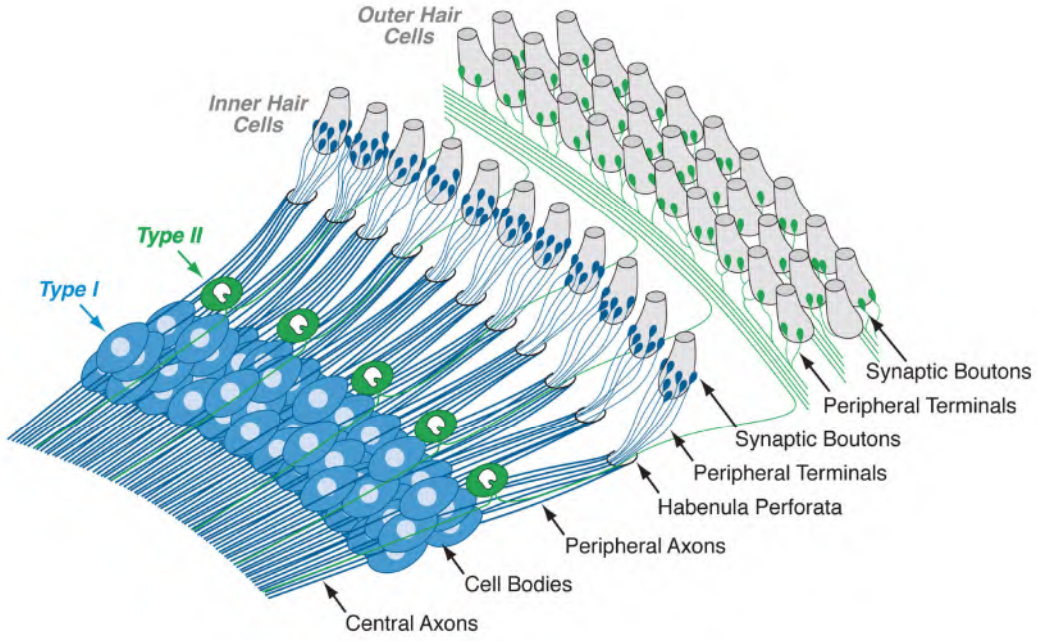

Figure 3. Innervation patterns of type I and type II auditory nerve fibers on inner and outer hair cells, respectively. Central and peripheral axons of type I cells are myelinated, whereas axons of type II neurons are unmyelinated. Peripheral terminals of type I and type II cells are unmyelinated within the organ of Corti, i.e. beyond the habenula perforata.

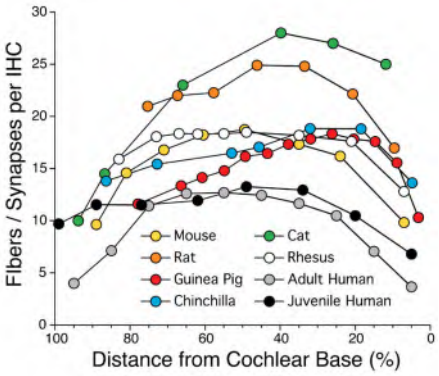

Figure 4. Normal density of auditory nerve fibers along the cochlear spiral. Data from the mouse, rat, guinea pig, chinchilla, rhesus monkey, and adult human are from the Liberman lab and are based on confocal analysis of immunostained synapses from cochlear epithelial whole mounts such as in Figure 5. Cat data are from a serial-section ultrastructural study[77]. Data from juvenile human are based on light-microscopic counts of peripheral axons from a 7-year-old[42]. Deviation between the two sets of human data at low frequencies may arise because ANFs in apical cochlear regions often form two synapses each[11].

octave-frequency intervals, typically 0.25, 0.5, 1, 2, 4, and 8 kHz (middle C is ~0.25 kHz, and the highest note on the piano is ~4 kHz). Human hearing is normally most sensitive near 1 kHz, where average sound pressure at threshold in young adults is 2×10^{-5} newtons/m^2, which is defined as 0 dB SPL (decibels sound pressure level). The dB scale is logarithmic, and each 20 dB increment corresponds to a 10-fold increase in the amplitude of the sound wave. The ear has an enormous dynamic range: loudness grows monotonically over at least a 100 dB range ($10^5 \times$ threshold pressure) and the threshold of pain is cited as 140 dB SPL ($10^7 \times$ threshold pressure)[18].

Cross-sectional studies in the 1960s documented the rise in audiometric thresholds with increasing years of exposure in noisy factories[19], where, prior to federal regulation of workplace noise, SPLs were in excess of 100 dB SPL (current regulations limit an 8-hour workday exposure to 85 dB SPL A-weighted). In its early stages, NIHL is often seen as a "notch" (i.e. threshold elevation) in the audiogram at 4 kHz. As exposure-time accumulates, the hearing loss extends to 8 kHz, and ultimately the audiogram can reveal no hearing sensation above 1 or 2 kHz, even at the highest sound pressures tested. AHL, as documented in cross-sectional studies, also affects the high frequencies first and can often lead to high-frequency deafness similar to that in advanced NIHL[20].

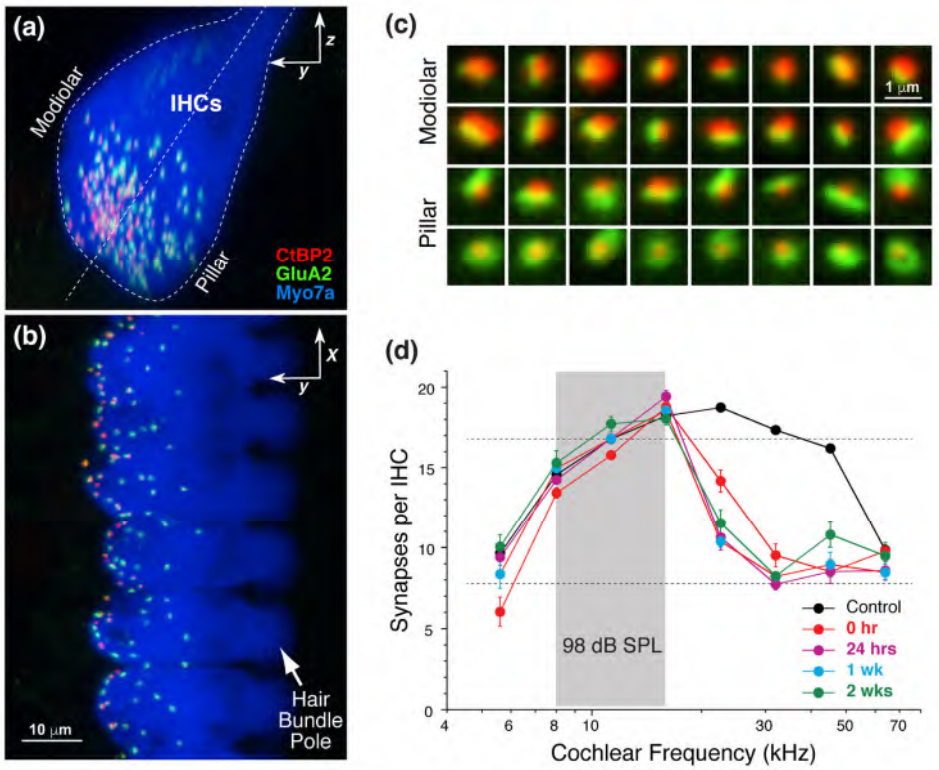

Figure 5. Noise-induced cochlear synaptopathy in the mouse. (**a**,**b**) Confocal images of mouse inner hair cells (myosin 7a – blue) immunostained for pre- and post-synaptic markers (CtBP2 – red, GluA2 – green) to reveal the synaptic contacts. **Panel (b)** shows the maximum projection of a focal series through six adjacent inner hair cells; **Panel (a)** shows the same image stack projected into the orthogonal plane to show a cross-sectional view like that schematized in Figure 2a. (**c**) High-power views of 32 synaptic puncta, segregated according to position on the inner hair cell (IHC) (modiolar versus pillar, see Figure 2a): low spontaneous discharge rate (SR) synapses are found on the modiolar side and have larger ribbons and smaller glutamate receptor patches. (**d**) Synaptic counts on inner hair cells from noise-exposed ears at several post-exposure times (from 38). The exposure (octave band noise at 98 decibels sound pressure level [dB SPL] for 2 hours) produced only a transient threshold elevation and no loss of hair cells.

At extremely high sound pressures, such as in blast injury (>180 dB SPL peak), there can be eardrum rupture and disarticulation of the ossicles[21]. However, for continuous-noise exposures at sound pressures like those in even the noisiest pre-regulation factories, damage is restricted to the inner ear, and OHCs are particularly vulnerable[2]. Complete loss of OHCs will elevate thresholds by 40–60 dB[22]. Loss of IHCs will silence all sound-evoked activity from affected cochlear regions[2]. Many surviving IHCs and OHCs suffer stereocilia damage that compromises function and can produce larger threshold shifts than predicted by the number of lost hair cells alone[23]. In animal studies, a single 2-hour exposure at 115 dB SPL can destroy all IHCs and OHCs throughout the basal (high-frequency) half of the cochlear spiral[2,24]. Fortunately, humans may be somewhat less vulnerable to noise than are smaller mammals, requiring higher SPLs or longer exposures to produce comparable damage[25]. Nevertheless, human ears with advanced NIHL or AHL also show extensive hair cell loss throughout the high-frequency cochlear regions[26].

Cochlear synaptopathy in NIHL and AHL

Although hair cell damage and death can be seen in minutes to hours after acoustic overexposure, death of spiral ganglion cells (the cell bodies of ANFs) is delayed by months to years[27]. This observation led to the dogma that hair cells are the primary target of noise damage and that neurons die only secondarily to loss of their peripheral synapses[5]. It has been known since the early 1980s that noise can lead to severe swelling of ANF terminals at their IHC synapses when examined within 24 hours post exposure[28,29]. This swelling, often accompanied by membrane rupture and loss of cytoplasmic contents, appears to be a kind of glutamate excitotoxicity, as it can be mimicked by cochlear perfusion of glutamate agonists and partially blocked by perfusion of glutamate antagonists[30,31]. However, ANF terminal swelling can be observed in ears with temporary threshold shifts (TTSs), and it disappears within a few days as thresholds recover. This threshold recovery led to the idea that neural connections recover or regenerate after noise damage, so long as the hair cells survive[32].

However, for years, no one counted ANF terminals in recovered ears because these unmyelinated endings and their synaptic connections are invisible in routine light-microscopic material (Figure 2a), and the serial-section ultrastructural analysis required to count them is extremely labor intensive[33]. Furthermore, threshold recovery, *per se*, is not proof of synaptic recovery. Cochlear function in these animal experiments is measured by recording ensemble ANF activity in response to brief tone bursts via metal electrodes on the cochlear capsule (compound action potential [CAP]) or in the skin of the external ear (auditory brainstem responses [ABRs]). Thresholds for these "gross" neural potentials are very sensitive to OHC damage, which can severely attenuate sound-evoked cochlear vibrations, but extremely insensitive to subtotal neural degeneration. This is because loss of ANFs and their contributions to the ensemble response can be readily compensated for, especially near threshold, by small increases in stimulus level, which recruit more responding fibers by spreading sound-evoked vibrations farther along the mechanically tuned cochlear spiral.

Thus, for many years, the question of whether or not noise destroys ANF synapses on surviving IHCs was not pursued. Then, my colleague Sharon Kujawa asked me to collaborate on a study of the interaction between NIHL and AHL. She exposed mice as young adults to a noise designed to produce a modest (40 dB) permanent threshold shift (PTS) and then let them age for 2 years to see if the cochlea deteriorated more rapidly in exposed versus unexposed animals. No prior work, to our knowledge, had followed animals for so long post exposure. Two years later, the noise-exposed mice showed ~50% loss of spiral ganglion cells in the basal half of the cochlea versus <5% in age-matched controls despite no significant loss of IHCs or OHCs in either group[34]. Thinking back to the work on acute noise-induced ANF terminal swelling, we speculated that the exposure in our mice might be causing immediate and irreversible synaptic damage, which was revealed only by the extremely slow death of the disconnected spiral ganglion cells.

To pursue the question, we modified published immunostaining protocols to allow rapid quantification of ANF synaptic contacts in the light microscope[35]. Each ANF contacts a single IHC via a single terminal bouton (Figure 2 and Figure 3), forming a synaptic plaque containing (typically) a single pre-synaptic ribbon[33,36]. Thus, cochleae immunostained for a ribbon protein (CtBP2, red) and a glutamate receptor subtype (GluA2, 3, or 4, green) show pairs of closely apposed red and green, pre- and post-synaptic puncta (Figure 5). Counts of puncta pairs from images acquired with confocal microscopy closely match values for ANF/IHC synapses in mice seen in a serial section ultrastructural analysis[36] and thus provide a rapid and robust measure of synaptic integrity in the IHC area. Each IHC is contacted by 4–28 ANFs depending on the species and cochlear location (Figure 4): although humans have fewer ANFs per IHC than do smaller mammals, the number of ANFs per cochlea is greater because our cochlea is much longer and has many more IHCs.

We now know that even exposures producing only a TTS, and leaving all hair cells intact, can destroy up to 50% of IHC synapses across large cochlear regions (Figure 5D). The damage is seen at cochlear regions tuned to frequencies higher than the exposure band because cochlear mechanics are non-linear: the region maximally stimulated at low SPLs (which defines "cochlear frequency") is apical to the region maximally stimulated at high SPLs[37]. The synaptic loss appears immediately after the noise[38] and, in the mouse, only worsens with increasing post-exposure time[39]. In guinea pigs, there is partial post-exposure recovery of synaptic counts, but this may represent transient down- and up-regulation of ribbon or receptor proteins rather than degeneration and regeneration of synaptic contacts. This widespread synaptic loss in the absence of significant hair cell loss has been replicated in noise-exposed rats, guinea pigs, chinchillas, and monkeys (for review, see 40). Synaptopathy also appears in ears exposed to ototoxic drugs such as aminoglycoside antibiotics; significant loss of IHC synapses appears at doses below those causing hair cell loss or threshold shifts[41]. Synaptopathy also appears in AHL: aging mice show synaptic loss before OHC loss (and the associated threshold shifts)[41], and surviving IHCs at the end of the mouse lifespan have lost ~50% of ANF synapses[38,41]. Normal-aging humans, i.e. those without explicit otologic disease, can also show dramatic cochlear neuropathy in regions of minimal hair cell loss[42]: e.g. one 89-year-old ear retained only ~20% of the normal complement of ANF contacts despite minimal loss of either IHCs or OHCs[12].

The mechanisms underlying noise-induced synaptic damage have not been clarified beyond the cochlear perfusion studies of glutamate excitotoxicity in the 1980s[30,31]. Recent work showing that synaptopathy also occurs after a single high-intensity shockwave[43] suggests that prolonged overexposure of the post-synaptic membrane to glutamate may not be required. Furthermore, it is unclear whether noise-induced, age-related, and drug-induced synaptopathy all share the same mechanism.

Hidden hearing loss and problems hearing in noise

Regardless of underlying mechanisms, emerging evidence suggests that surviving IHCs are partly or largely disconnected from their primary sensory fibers in many types of acquired sensorineural hearing loss. This synaptopathy has been called "hidden hearing loss"[44] because the damage is not visible in routine cochlear histopathology and because primary neural degeneration does not significantly affect the threshold audiogram until it exceeds ~80%[45,46]. Although not needed for pure-tone detection in quiet environments, a full complement of ANFs is likely required for more difficult listening tasks.

Recordings from single ANFs in normal and noise-exposed animals suggest how synaptopathy might especially compromise hearing in noisy environments. In the normal ear, ANFs comprise at least two subgroups: low-threshold fibers with high spontaneous discharge rates (SRs) and high-threshold fibers with low SRs (Figure 2c), constituting ~60% and 40% of the ANF population, respectively[47–49]. Although both high- and low-SR fibers can contact the same IHC (Figure 2b), their synapses are spatially segregated around the IHC circumference (Figure 2 and Figure 5) and their central projections are different[50–52]. Their sensitivity differences likely arise from a combination of pre- and post-synaptic differences in channel expression and input resistance, respectively[53,54]. Single-fiber recording studies have shown that

low-SR synapses are the first to degenerate in AHL[55], NIHL[56], and at least one kind of drug ototoxicity[57]. The reasons for their heightened vulnerability are not clear but may be related to the paucity of mitochondria in their peripheral terminals[33], as mitochondria, in supplying ATP for Ca^{2+} pumps, are critical to the regulation of intracellular Ca^{2+}, and Ca^{2+} overload is critical in the genesis of glutamate excitotoxicity[58]. Persistent abnormalities in some high-SR responses have also been reported in synaptopathic guinea pigs[59].

As shown in Figure 2d, the high-threshold, low-SR fibers normally extend the dynamic range of the auditory periphery[60,61], but their loss should not affect threshold detection of stimuli in an otherwise quiet environment. In the presence of continuous masking noise, however, their contributions become more critical, and their loss becomes more handicapping. By virtue of their higher thresholds, low-SR fibers are more resistant to "masking" by continuous noise[62]. As the noise level rises, low-threshold, high-SR fibers are driven to "saturated" discharge rate, leaving only the high-threshold, low-SR fibers to carry information about stimuli embedded in the noise.

Hidden hearing loss in humans: diagnosis and treatment

Difficulty hearing in noise is a major complaint of people with sensorineural hearing loss, and it has long been known that two people with the same audiogram, whether normal or abnormal, can perform differently on speech-in-noise tests. Prior to the discovery of hidden hearing loss, these differences were ascribed largely to differences in central auditory processing. A few human histopathological studies suggest that cochlear synaptopathy is an important component of human sensorineural hearing loss, and one even suggests that it is correlated with word-recognition scores[63]. However, the inner ear cannot be biopsied, so enhanced diagnostic tests are needed to screen living subjects.

In mouse studies, we showed that suprathreshold amplitudes of ABR wave 1, the summed onset responses of ANFs, were well correlated with the degree of cochlear synaptopathy, so long as cochlear sensitivity was not compromised due to OHC dysfunction[6,41]. Once thresholds are elevated, it is difficult to separate changes due to synaptopathy from those due to hair-cell damage. Auditory evoked potentials such as ABRs are easily measured in human subjects from scalp and/or ear-canal electrodes. In a recent study of young adults with normal audiograms, we found a correlation between performance on a difficult speech-in-noise test and alterations in auditory evoked potentials that were consistent with cochlear synaptopathy[64]. Having purposely sought out subjects who abused their ears (aspiring musicians who never wore ear protection) and those who routinely protected their ears, we also noted a correlation between ear abuse and poorer performance on speech-in-noise tests. Other studies have shown correlations among normal-threshold young subjects between the ability to perform complex listening tasks and alterations in ABRs that suggest a peripheral rather than a central origin[65]. A recent study of military veterans with normal audiograms has also found a correlation between ABR wave 1 amplitudes and noise-exposure history[66], while another recent study of "normal-hearing" subjects in the UK failed to find such a correlation[67]. However, different metrics of noise history were used, and neither study correlated the electrophysiological results with performance on speech-in-noise tasks.

Clearly, more work is needed in this area. However, existing data from humans and animals make it clear that significant cochlear neural damage can occur without hair cell damage and thus can hide behind a normal audiogram. This neural damage is likely to be a handicap in difficult listening situations, especially as overt hearing loss (i.e. threshold elevation and hair cell damage) is added to the mix. Since existing federal guidelines on workplace noise exposure were derived based on the assumption that exposures producing no PTSs are benign[68], a careful re-evaluation of these guidelines is warranted if hidden hearing loss is to be prevented as well.

An exciting aspect of this work is the notion that some of the hearing handicap in sensorineural hearing loss might be treatable or preventable[69]. In mammalian cochleae, including those in humans, hair cells and cochlear neurons are post-mitotic, and damaged or lost elements are never replaced[70]. Although limited hair cell regeneration via transdifferentiation of remaining support cells has been demonstrated in animal models[71], the repair of cochlear synaptopathy is arguably simpler because there is an extended therapeutic window in which the hair cell targets as well as the spiral ganglions and their central axons survive[6]. Multiple animal studies have shown that local delivery of neurotrophins, endogenous players in the signaling pathways involved in neuronal development and maintenance, can elicit neurite extension from spiral ganglion cells even in the adult mammalian ear[72]. Several recent studies in the mouse and guinea pig have shown that at least within 24 hours post exposure, neurotrophin delivery can repair the noise-induced synaptic damage as it restores ABR amplitudes[7,73,74]. Regeneration is likely more difficult at longer post-exposure times, but even in humans the distance from cell body to hair cell is <0.5 mm, and spiral ganglion cell death must be extremely slow because cochlear implants inserted years after deafness onset still provide useful hearing[75]. Thus, it does not seem too far-fetched to imagine that there could be therapies for hidden hearing loss on the horizon.

Competing interests

The author is a scientific founder of Decibel Therapeutics.

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Behavioral/Systems/Cognitive

Acceleration of Age-Related Hearing Loss by Early Noise Exposure: Evidence of a Misspent Youth

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Age-related and noise-induced hearing losses in humans are multifactorial, with contributions from, and potential interactions among, numerous variables that can shape final outcome. A recent retrospective clinical study suggests an age–noise interaction that exacerbates age-related hearing loss in previously noise-damaged ears (Gates et al., 2000). Here, we address the issue in an animal model by comparing noise-induced and age-related hearing loss (NIHL; AHL) in groups of CBA/CaJ mice exposed identically (8–16 kHz noise band at 100 dB sound pressure level for 2 h) but at different ages (4–124 weeks) and held with unexposed cohorts for different postexposure times (2–96 weeks). When evaluated 2 weeks after exposure, maximum threshold shifts in young-exposed animals (4–8 weeks) were 40–50 dB; older-exposed animals (≥16 weeks) showed essentially no shift at the same postexposure time. However, when held for long postexposure times, animals with previous exposure demonstrated AHL and histopathology fundamentally unlike unexposed, aging animals or old-exposed animals held for 2 weeks only. Specifically, they showed substantial, ongoing deterioration of cochlear neural responses, without additional change in preneural responses, and corresponding histologic evidence of primary neural degeneration throughout the cochlea. This was true particularly for young-exposed animals; however, delayed neuropathy was observed in all noise-exposed animals held 96 weeks after exposure, even those that showed no NIHL 2 weeks after exposure. Data suggest that pathologic but sublethal changes initiated by early noise exposure render the inner ears significantly more vulnerable to aging.

Key words: **mouse; noise-induced hearing loss; age-related hearing loss; primary neural degeneration; neuropathy; auditory**

Introduction

Hearing losses that accumulate with chronic exposure to high-level sound [noise-induced hearing loss (NIHL)] and those we attribute to age [age-related hearing loss (AHL) or presbycusis] are major health problems. They are common, their consequences are permanent, and their impact on human communication and quality of life is significant. NIHL and AHL often coexist in the same ear; however, the conditions under which these forms of hearing loss interact and the mechanisms by which they do so remain poorly understood.

In a recent review of longitudinal hearing loss data from a large cohort of men in the Framingham Heart Study, Gates et al. (2000) observed that, in ears with presumed cochlear damage from previous noise exposure, subsequent hearing loss progression with age was exacerbated at frequencies outside the original NIHL. This observation suggests that ears with noise damage age differently from those without.

This issue of AHL/NIHL interaction has obvious public health significance (Gates et al., 2000; Rosenhall, 2003; Lee et al., 2005) given the high prevalence of noise exposure in and the aging of our society. Concern about long-term effects of noise exposure in young ears is heightened by reports of increasing NIHL prevalence earlier in life (Wallhagen et al., 1997; National Institutes of Health, 2000; Folmer et al., 2002). However, addressing the question in human studies is difficult. Hearing losses in noise-exposed and/or aging ears are highly variable (Gates and Mills, 2005). This variability may arise from underlying differences in actual noise exposures, as well as the influence of other intrinsic and environmental variables that produce hearing loss on their own or alter NIHL vulnerability (Henderson et al., 1993). Such variables do not lend themselves easily to retrospective quantification. Similarly, variability in age of onset, progression, and severity of AHL may be influenced by genetic factors (Gates et al., 1999; DeStefano et al., 2003) and heterogeneity in underlying pathology (Schuknecht and Gacek, 1993), as well as the variable contribution of other insults accumulated over the course of a lifetime (Lutman and Spencer, 1990; Karlsson et al., 1997). This variability has complicated our conduct and interpretation of investigations of NIHL and AHL in humans.

Many of these sources of variability can be eliminated in a laboratory setting using mouse models, in which rigorous genetic and experimental control can be achieved. Indeed, intersubject variability in NIHL within genetically inbred mouse strains is significantly lower than that seen in outbred laboratory animals

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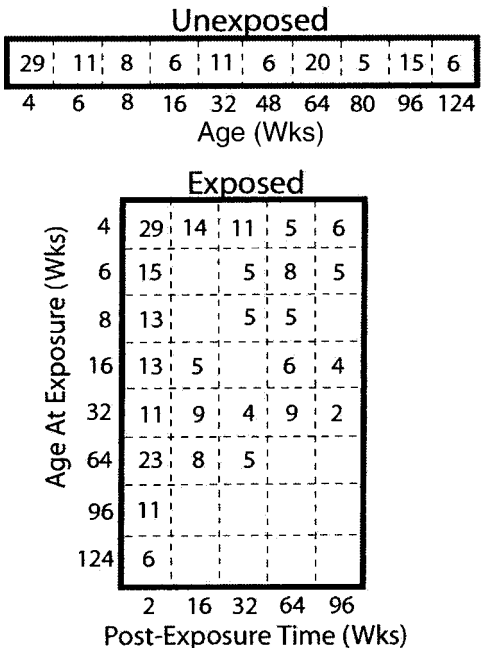
Table 1. Matrix showing the numbers of animals in each of the groups in the present study



For the "Unexposed" groups, the age indicates the age at final test. For the "Exposed" groups, the row number indicates the age at noise exposure, and the column number indicates the postexposure survival.

(Yoshida et al., 2000; Wang et al., 2002) and humans. Furthermore, important between-strain differences in vulnerability to NIHL and AHL have been identified (Li, 1992; Erway et al., 1993; Johnson et al., 1997; Yoshida et al., 2000; Davis et al., 2003; Candreia et al., 2004). Here, we address the issue of AHL/NIHL interactions directly by comparing NIHL and AHL in groups of CBA/CaJ mice exposed identically but at different ages and held without additional exposure with unexposed cohorts for different postexposure times. Our results suggest that previous noise exposure has significant, deleterious effects on the nature and progression of an age-related hearing loss.

Materials and Methods

Animals and groups. Mice (CBA/CaJ) of either sex were entered into the protocol at various target ages (4, 6, 8, 16, 32, 64, 96, and 124 weeks; ±5% deviations from targets allowed). Noise exposures were delivered to subsets of animals from each group, and they, along with their unexposed age-matched controls, were held without additional treatment for various postexposure times (2, 16, 32, 64, and 96 weeks). Using this strategy, threshold shifts can be compared for animals (1) exposed at the same age but held for different postexposure times, (2) exposed at different ages but held for identical postexposure times, and (3) tested at nominally the same age but exposed and held for different times.

Sound levels in the animal care facility room in which the animals were held were monitored periodically using a data-logging noise dosimeter (NoisePro DLX; Quest Technologies, Oconomowoc, WI). In the periods of monitoring, 24 h Leq [the equivalent continuous sound level (Leq) is a logarithmic average of noise levels in a given area over a stated period of time (e.g., 24 h, 1 year, etc.)] values ranged between ~50 and 60 dB sound pressure level (SPL) at the level of the cages. In a final experiment, threshold shifts (NIHL, AHL, and aggregate) were quantified by auditory brainstem responses (ABRs) and distortion product otoacoustic emissions (DPOAEs), and cochlear tissues were recovered from representative animals to characterize the histopathology. The numbers of animals in each group are provided in Table 1. All procedures were approved by the Animal Care Committee of the Massachusetts Eye and Ear Infirmary.

Acoustic overexposures. Exposures (8–16 kHz octave-band noise, 100 dB SPL, 2 h) were delivered to awake animals held unrestrained within small cells in a subdivided cage (one animal per cell). The noise was generated by a waveform generator (model WG1; Tucker-Davis Technologies, Alachua, FL), filtered (8–16 kHz bandpass, >60 dB/octave slope; Frequency Devices, Haverhill, MA), amplified (D-75 power amplifier; Crown Audio, Elkhart, IN), and delivered (compression driver; JBL, Northridge, CA) through an exponential horn extending into a small, reverberant exposure chamber. The subdivided cage was suspended directly below the horn of the sound-delivery loudspeaker. Noise calibration to target SPL was performed immediately before each exposure session. Sound pressure levels, measured by placing a quarter-inch condenser microphone within each of the four subdivisions of the cage, varied by <1 dB. Typically, one young (4–8 weeks) animal was included in each exposure session as an additional control for the noise-exposed groups over the many months necessary to accomplish these experiments.

Functional assays. Physiologic tests were conducted in an acoustically and electrically shielded chamber. Animals were anesthetized (ketamine, 100 mg/kg, i.p.; xylazine, 10 mg/kg, i.p.), with booster injections (half of the original dose) given as needed. Temperature was maintained near 37°C by heating the air in the experimental chamber. A small V-shaped incision was made in the cartilaginous external canal, widening its opening to facilitate unobstructed viewing of the tympanic membrane and optimum placement of the sound-delivery system.

Stimuli were created and responses were monitored using 16-bit analog-to-digital and digital-to-analog boards (model 6102; National Instruments, Austin, TX) controlled in a LabVIEW environment by a personal computer workstation. Signals used to elicit ABRs and DPOAEs were delivered to the ear using the same custom coupler. The coupler accommodates two transducers (model EC1; Tucker-Davis Technologies) and an EK3103 electret microphone (Knowles Electronics, Itasca, IL) to measure ear-canal sound pressure via a probe tube concentric with the sound-delivery tube. Calibration curves for the probe microphone enabled conversion from voltage to decibel SPL at the probe tip (in decibels relative to 20 μPa).

ABRs were recorded via subdermal needle electrodes (vertex, ventrolateral to left pinna). Stimuli were 5 ms tone pips (0.5 ms rise/fall), at frequencies between 5.6 and 45.2 kHz (half-octave steps) delivered at levels below threshold to 80 dB SPL in 5 dB steps. Responses were amplified (10,000×), filtered (0.3–3 kHz), digitized, and averaged (across 1024 responses at each frequency–level combination; artifact reject, 15 μV peak-to-peak). On visual inspection of stacked waveforms, threshold was defined as the lowest stimulus level at which response peaks were repeatably present. Responses absent at the highest level of stimulation (80 dB SPL) were assigned a threshold value 5 dB higher. Response values (thresholds, peak-to-peak amplitudes, and N1 latencies) and waveforms were stored to disk for off-line analysis.

DPOAEs were recorded as amplitude versus level functions (L_1, 20–75 or 80 dB SPL in 5 dB steps; L_2, $L_1 - 10$) at f_2 frequencies ($f_2/f_1 = 1.2$) between 5.6 and 45.2 kHz (half-octave spacing). Ear-canal sound pressure was amplified and digitally sampled at 4 μs intervals. DPOAE amplitude at $2f_1 - f_2$ and surrounding noise floor ±50 Hz of the DPOAE were extracted from the averaged waveforms of ear-canal sound pressure. DPOAE and noise floor values and averaged waveforms were stored to disk. Responses were analyzed as iso-response functions relative to L2 levels required to generate DPOAEs of −5 dB SPL (Kujawa and Liberman, 1999). Stimulus levels were kept below 80 dB SPL to avoid system-generated distortion. When responses were absent at the maximum levels presented, a threshold value 5 dB higher was again assigned. The ABR stimulus-level maximum was set to 80 dB SPL for consistency.

Histologic preparation and analyses. After final physiological testing, selected animals were deeply anesthetized, and cochlear tissues were retrieved for histologic processing and evaluation. Ears were prepared by a thick-sectioning technique allowing thorough light microscopic evaluation of all structures of the murine cochlea (Hequembourg and Liberman, 2001). In brief, animals were perfused intracardially with 2.5%

glutaraldehyde and 1.5% paraformaldehyde in phosphate buffer. Both cochleas were extracted, and the round and oval windows were opened to allow intra-labyrinthine perfusion of the same fixative. After overnight postfixation in the same fixative at 4°C, the cochleas were osmicated (1% OsO_4 in dH_2O) for 1 h and then decalcified (0.1 M EDTA with 0.4% glutaraldehyde) for 2–3 d. Decalcified cochleas were dehydrated in ethanol and propylene oxide, embedded in Araldite resins, and sectioned at 40 μm on a Historange with a carbide steel knife. Sections were mounted in Permount on microscope slides and coverslipped.

Cochlear structures were assessed at the light microscopic level for signs of histopathology. We used a semiquantitative rating scale for assessment of fractional cellular survival of the sensory cells and their afferent innervation (spiral ganglion cells), as well as for cellular elements within three critical accessory structures of the cochlear duct: the stria vascularis, spiral ligament, and spiral limbus. The examiner was blind to age-exposure status.

Results

The CBA/CaJ mouse was chosen for this study because, in contrast to many other inbred strains (Zheng et al., 1999), it maintains good threshold sensitivity well into old age (Henry and Chole, 1980; Hunter and Willott, 1987; Jimenez et al., 1999). Two metrics of auditory function were used to measure threshold sensitivity: DPOAEs and ABRs. DPOAEs arise from normal cochlear nonlinearities generated by transduction in outer hair cells and are not affected by damage to inner hair cells or cochlear neurons (Liberman et al., 1997). ABRs represent the summed activity of auditory neurons and thus require functional integrity of all preneural elements (including both outer and inner hair cells), as well as their afferent innervation. Comparison of threshold shifts seen via the two measures thus provides important clues as to the site(s) of dysfunction. Young adult animals tested here had baseline thresholds similar to those reported previously (Henry, 2004).

NIHL vulnerability varies with age at exposure

Effects of noise exposure include reversible and irreversible components. After exposures that are intense enough to produce permanent effects, thresholds recover exponentially with increasing postexposure time and reach steady state within ~2 weeks (Miller et al., 1963). Thus, to evaluate vulnerability to permanent NIHL, threshold shifts were initially measured at 2 weeks after exposure.

Age at exposure was varied systematically while holding all other exposure parameters (sound pressure, duration, bandwidth, etc.) constant, to examine its influence on NIHL. Figure 1 shows mean threshold shifts for animals at two extremes of our exposure-age range (4 vs 96 weeks). Young-exposed animals show a maximum threshold shift of ~40 dB at the frequency (16 kHz) corresponding to the upper edge of the exposure band (8–16 kHz). In contrast, old-exposed ears show no threshold elevation. Similar results were obtained with ABR and DPOAE measures, consistent with the notion that the functionally important changes in these ears involve the outer hair cells, which are among the most vulnerable structures in the inner ear (Hamernik et al., 1989; Saunders et al., 1991; Dallos, 1992).

A more detailed look at the relationship between age and noise vulnerability is offered in Figure 2. Here, maximum threshold shift at 2 weeks (i.e., shift at 16 kHz) is plotted versus age at exposure for all groups in the present study (Fig. 2*A*,*B*). The data show a dramatic shift in vulnerability between 8 and 16 weeks: there is little difference among the young-exposed groups (4, 6, and 8 weeks) and little difference among the older-exposed groups (16, 32, 64, and 124 weeks) at this 2 week postexposure

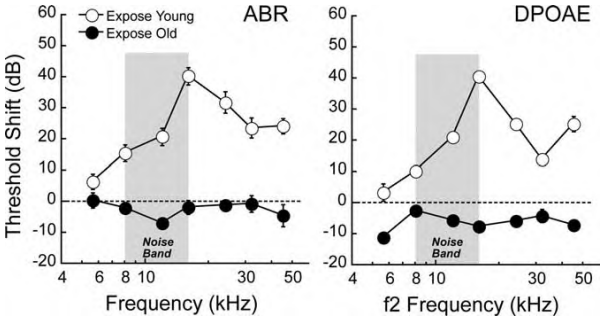


Figure 1. Young (4–8 weeks) mice are more vulnerable to noise damage than old (96 weeks) mice. Each age group was exposed to high-level noise, and threshold shifts were measured by ABR and DPOAE 2 weeks later. Threshold shifts (calculated relative to age-matched, unexposed cohorts) are greater in young-exposed ears by both measures. Data are expressed as means ± SE. For the numbers of animals in each group, see Table 1. The gray bar denotes the pass band of the noise-exposure stimulus.

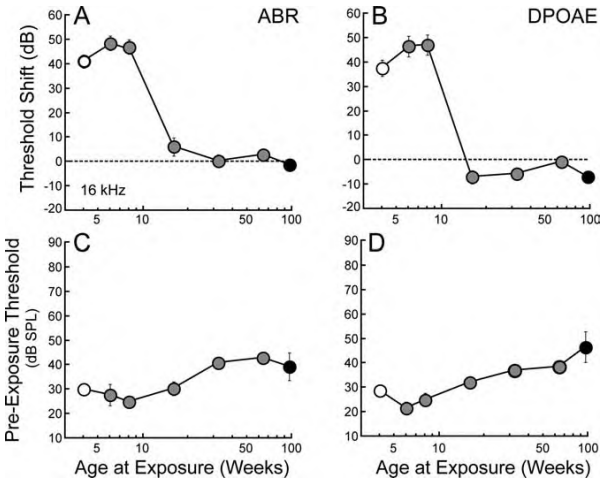


Figure 2. Vulnerability to noise decreases dramatically between 8 and 16 weeks of age. ***A***, ***B***, Maximum threshold shifts (i.e., shifts at 16 kHz) seen at 2 weeks after exposure by ABR (***A***) and DPOAE (***B***) for all ages at exposure. ***C***, ***D***, In unexposed control ears, thresholds at 16 kHz do not show large change between 8 and 16 weeks. Data are means ± SE and are plotted as a function of age on a logarithmic scale. For the numbers of animals in each group, see Table 1.

time. DPOAE and ABR data are virtually identical, and there were no statistically significant gender differences in NIHL.

It is important to consider the age-related progression in preexposure thresholds over the same timespan, shown in Figure 2, *C* and *D*. The precipitous drop in maximum noise-induced threshold shift between 8 and 16 weeks has no obvious counterpart in a change in baseline sensitivity: our data from unexposed groups show that sensitivity at 16 kHz changes <5 and <10 dB across the entire frequency range of test over the same period of time.

AHL is exacerbated by previous noise exposure

To evaluate interactions between NIHL and subsequent AHL, we tracked thresholds in noise-exposed versus unexposed ears with increasing postexposure survival, out to the lifespan of the mouse (~2.5 years).

First, consider animals exposed to noise at 4 weeks. When measured 2 weeks later, threshold shifts by both ABR and DPOAE peaked at 40 dB at 16 kHz (open circles in Fig. 3*A*,*B* are

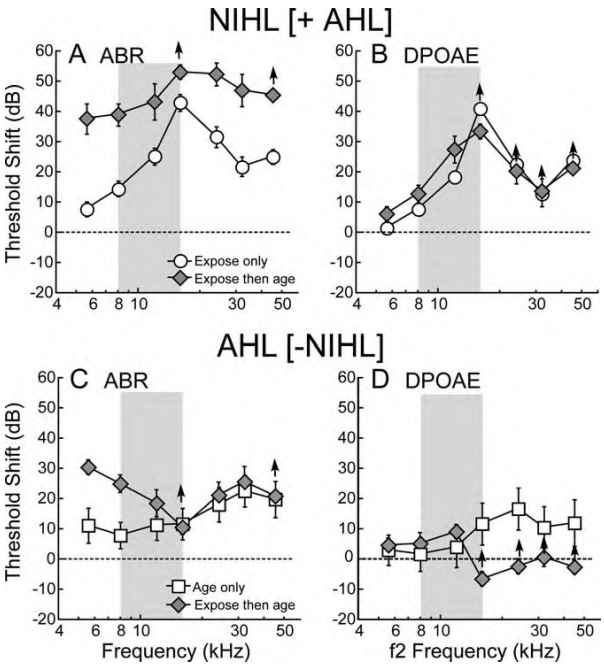


Figure 3. Early NIHL exacerbates AHL when measured by ABR (***A***, ***C***) but not by DPOAE (***B***, ***D***). ***A***, ***B***, NIHL in animals exposed at 6 weeks (white circles; replotted from Fig. 1) is defined as thresholds at 2 weeks after exposure relative to unexposed 6 week controls; 96 weeks later, aggregate NIHL/AHL in animals exposed at 6 weeks is also calculated relative to unexposed 6 week controls. ***C***, ***D***, AHL in unexposed animals (white squares) is simply the difference between thresholds at 102 versus 6 weeks; AHL for the noise-exposed group (gray diamonds) removes the initial NIHL component, i.e., it is the difference between thresholds at 96 versus 2 weeks after exposure (the difference between the curves in ***A*** and ***B***). Data are means ± SE. For the numbers of animals in each group, see Table 1. The arrows above the points indicate that at least 50% of animals from this group at this frequency lacked responses at the highest SPLs presented; thus, the threshold shift may be underestimated. For additional explanation, see Materials and Methods.

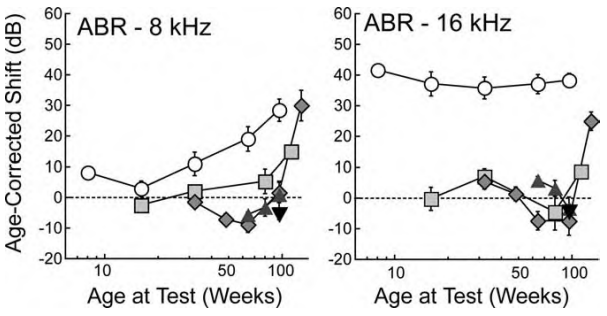


Figure 4. Progressive threshold shifts as a function of age in animals initially exposed to noise at different ages: 6 weeks (white circles), 16 weeks (gray squares), 32 weeks (gray diamonds), 64 weeks (gray triangles), or 96 weeks (black triangles). Shifts are shown at 16 kHz (right), the frequency of maximum initial shift, and 8 kHz (left), a frequency showing minimal initial shift. Age-corrected shifts are defined as the difference between the measured threshold and the thresholds of unexposed animals of similar age. Data are plotted as a function of age at test; thus, an animal exposed at 16 weeks and held for 32 weeks will be plotted at 48 weeks of age. The numbers of animals in each group are given in Table 1.

replotted from Fig. 1*A*, *B*). When reexamined 96 weeks later, ABR threshold shifts had grown dramatically across the entire range of test frequencies, whereas DPOAE thresholds changed only slightly (Fig. 3*A*, *B*). This striking discrepancy between ABR and DPOAE shifts suggests that progressive age-related changes in the noise-damaged ear involve the inner hair cell and/or the auditory nerve to a greater degree than the outer hair cells or other structures contributing to the cochlear amplifier. The difference between threshold curves at 2 versus 96 weeks after exposure is a measure of the AHL in these young-exposed ears. As seen in Figure 3*C*, this AHL (filled squares) is significantly larger than that seen in unexposed ears (open squares) when evaluated by ABR. Thus, early noise exposure increases AHL, especially at frequencies below the region of maximum damage (e.g., 5.6 and 8.0 kHz), in which initial postexposure threshold shift was minimal. Note that the exacerbation of AHL at high frequencies may be even greater than suggested, given that both ABR and DPOAE measures of threshold shift "saturate" as the sound pressures required to elicit a response (in the noise-exposed groups) reach the maximum sound pressures tested (Fig. 3, upward arrows) (for additional explanation, see Materials and Methods). With respect to possible gender effects of AHL/NIHL interactions, the number of males in the unexposed, old group was too small ($n = 2$) to calculate meaningful threshold shifts.

To evaluate how the interaction between AHL and NIHL varies with age-of-exposure, we extract the ABR-based threshold shifts at 8 and 16 kHz from each exposed group at each postexposure age and "correct" for age by subtracting the corresponding threshold shift seen in age-matched, unexposed controls (Fig. 4). By this procedure, the "age-corrected shift" is a measure of the original noise-induced shift plus any additional hearing loss seen in the ABR response, above and beyond that expected attributable to aging alone. Consider first the data at 8 kHz. For the group exposed at 4 weeks (open circles), the age-corrected shift grows steadily with postexposure time to a maximum of ~25 dB at 96 weeks (the same value shown in Fig. 3*C* at 8 kHz), suggesting a strong interaction between NIHL and subsequent AHL. Data from the groups exposed at 16 and 32 weeks (Fig. 4*A*, squares and diamonds, respectively) also show interactions between NIHL and AHL at the longest postexposure holding times: the thresholds deteriorate after noise exposure more dramatically than in age-matched, unexposed counterparts. Thus, the long-term sequelae of noise exposure are visible regardless of whether the exposure occurred before or after the dramatic drop in vulnerability (at 8 vs 16 weeks) and even when the initial exposure led to threshold shifts, which were completely reversible in the short term (Fig. 1). Similar AHL/NIHL interactions are seen in the data at 16 kHz, except for the group exposed at 4 weeks wherein the threshold shifts may saturate, thus leading to an underestimate of the "additional" threshold shifts as these animals age.

AHL/NIHL interactions produce primary neural degeneration

When cochleae from young- or old-exposed animals were harvested 2 weeks after exposure and examined with age-matched, unexposed counterparts, the organ of Corti was intact; there was virtually no hair cell loss outside of the extreme high-frequency end of the cochlear spiral. Other cochlear structures, including the stria vascularis, spiral limbus, tectorial membrane, etc., did not appear pathologic in any systematic way (Figs. 5*A*, 6*A–C*). Such results are consistent with previous work (Liberman and Beil, 1979) demonstrating that noise-induced permanent threshold shifts on the order of 40 dB do not require hair cell loss but can occur with stereocilia damage alone (which was not evaluated in the present study).

Many of the noise-exposed ears showed cell loss among a small spatially distinct class of fibrocytes (type IV) within the spiral liga-

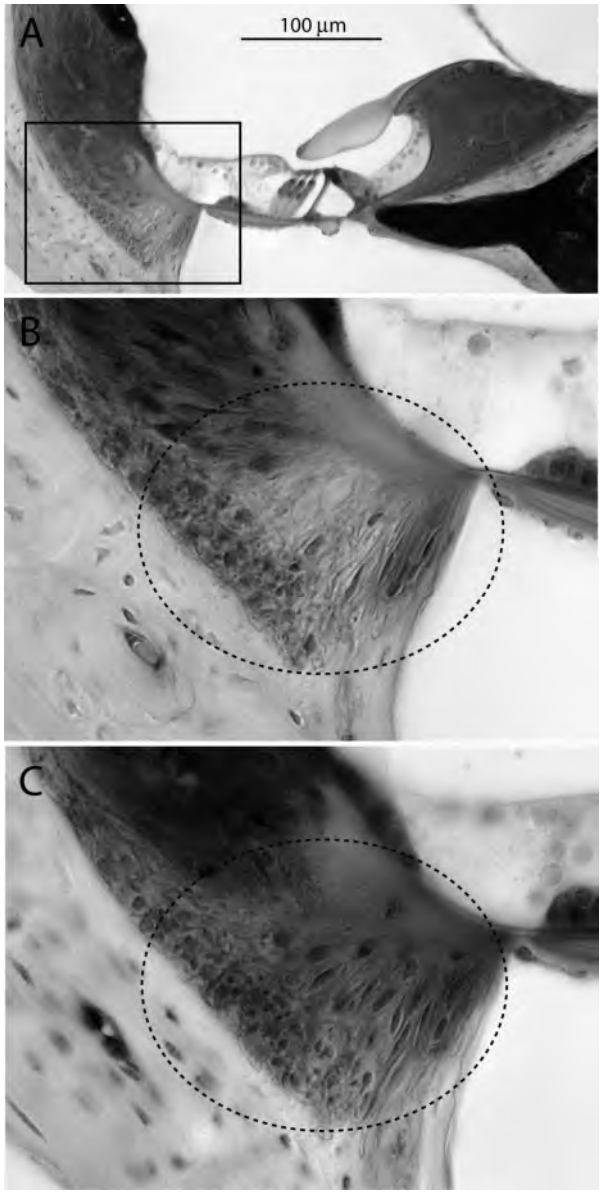


Figure 5. When examined 2 weeks after exposure, the only histopathology is loss of type IV fibrocytes: compare circled regions of ***B*** and ***C***. ***A*** and ***B*** show the upper basal turn of an ear exposed at 6 weeks and tissues processed at 8 weeks. The region of the high-power view in ***B*** is indicated by the box in ***A***. ***C*** shows the normal appearance of the type IV fibrocytes at the same cochlear region.

ment (Fig. 5, compare *B*, *C*). The presence or absence of type IV cells was not well correlated with the degree of threshold shift: as shown in Figure 8, estimated type IV loss was greater in ears exposed at 2 years than in those exposed at 6 weeks, although the former had no permanent NIHL, whereas the latter had a 40 dB shift. Previous studies have noted the vulnerability of the type IV cells and the lack of correlation with threshold shifts (Wang et al., 2002).

The most striking histopathologic change was a widespread loss of spiral ganglion cells, the cell bodies of cochlear nerve afferents, most of which make synaptic contact with inner hair cells. As illustrated by the micrographs in Figure 6, such neuronal loss was seen only in aged ears that were noise-exposed earlier in life; it was not seen in unexposed groups, regardless of age, nor in noise-exposed groups evaluated at short postexposure times. Because the neuronal loss was not associated with hair cell loss, it is considered a "primary" neural degeneration rather than occurring secondary to the hair cell degeneration. Even at the limits of resolution of the light microscope, the hair cells and supporting cells of the organ of Corti looked completely normal in most cochlear regions of all exposure groups: representative high-power differential interference contrast (DIC) images are shown in Figure 7. Based on previous studies at both the light and electron microscopic levels (Liberman and Dodds, 1984), it is likely that initial noise-induced threshold shift in our mice was attributable to stereocilia damage, especially on outer hair cells, which is not well resolved in the type of histological material used in this study.

These qualitative observations were quantified and systematically evaluated in an analysis by an observer blind to the age and exposure history of the tissue. Results of this analysis are shown in Figure 8, in which means and SEs are shown for fractional survival of inner and outer hair cells, spiral ganglion cells, and type IV fibrocytes in ears from representative groups in the present study. None of the groups showed significant loss of inner hair cells, and variable amounts of outer hair cell loss were seen but only in the more apical regions (primarily 6 and 14 kHz) and only in the older animals (regardless of exposure history). Apical outer hair cell loss has been reported previously in aging CBA/CaJ (Henry and Chole, 1980; Spongr et al., 1997) and CBA/J (Ohlemiller and Gagnon, 2004). Type IV fibrocyte loss was seen primarily in the high-frequency region (30 kHz) and only in the noise-exposed ears, with severity of loss greatest in ears surviving for longer postexposure times. Widespread loss of spiral ganglion cells was seen only in noise-exposed animals held for long postexposure times. In unexposed animals, there was modest loss (<20% on average) but only in the apex and only in old animals, consistent with previous studies of aging mice and rats (Keithley and Feldman, 1979, 1982; Dazert et al., 1996). In exposed animals, ganglion cell loss was not seen in the short-surviving ears, whether the age at exposure was 6 weeks ("Expose Young Test Young") or 124 weeks ("Expose Old Test Old"). In the long-surviving ears, the neuronal loss could be seen throughout the cochlea and was significant regardless of whether the ears were exposed at 6 weeks ("Expose Young Test Old") or at 16–32 weeks (data not shown).

Discussion

Critical period for noise vulnerability

Numerous studies of cochlear function have suggested a period of heightened sensitivity to insult from noise or ototoxic drugs during (Bock and Saunders, 1977; Bock and Seifter, 1978; Lenoir et al., 1979; Henley and Rybak, 1993) and beyond (Henry, 1982, 1983; Pujol, 1992) periods of obvious structural and functional maturation of the cochlea. In mouse, age-related shifts in NIHL vulnerability are well documented. In commonly used variants of CBA (CBA/J, CBA/Ca, and CBA/CaJ), noise vulnerability decreases with age (Henry, 1982, 1983; Li and Borg, 1993; Ohlemiller et al., 2000). Henry (1982) exposed CBA mice at 60, 90, 120, and 360 d and found a reduction in vulnerability as exposure age increased from 60 to 120 d (nominally 8 and 17 weeks). Present results are in good agreement with this observation.

Middle ear motion decreases with age (Doan et al., 1996; Rosowski et al., 2003), and less efficient transfer through the middle ear could decrease NIHL vulnerability. Direct measurements of sound transmission through the aging middle ear in CBA/CaJ (Rosowski et al., 2003) show that transmission losses may account for part of the sensitivity reduction (<6 dB) at frequencies above 16

kHz in old, unexposed ears. However, in the noise-exposure band used here (8–16 kHz), middle ear transmission changes by <2 dB between 8 and 96 weeks. Middle ear changes between 8 and 16 weeks must be significantly smaller and cannot underlie the dramatic change in noise vulnerability. Even a 2 dB transmission decrease could cause a 12 dB decrease in NIHL (Yoshida et al., 2000), i.e., much smaller than the 40 dB differences observed between 8 and 16 week animals (Fig. 1). Thus, the age-related shift in vulnerability must arise in the inner ear.

The inner ear is mature morphologically, and electrophysiologic properties of hair cells and gross cochlear response thresholds have stabilized by 4 weeks, the youngest animals studied here (Mikaelian et al., 1965; Lim and Anniko, 1985; Marcotti et al., 2003; Hafidi et al., 2005). Thresholds in the 8–16 kHz range are almost identical in 4- versus 16-week-old animals (Fig. 2); thus, the vulnerability shift has no obvious correlate in cochlear sensitivity. Indeed, apart from the dramatic shift in noise vulnerability, there is no reported change in cochlear structure or function over the critical time period from 8 to 16 weeks. It may be significant that mice reach sexual maturity ~6–8 weeks (first in females and then males); thus, endocrine changes may produce previously undetected changes in cochlear function that influence noise vulnerability. In the present series, no difference in preexposure thresholds was seen for young males versus females. Two studies, those of Guimaraes et al. (2004) and Henry (2004), report that, among older CBA mice, males show higher thresholds (i.e., more AHL) than females. Although no gender difference in noise vulnerability was observed here for short postexposure times, evaluation of possible gender influences on the progressive neuropathy of long-surviving animals is underway.

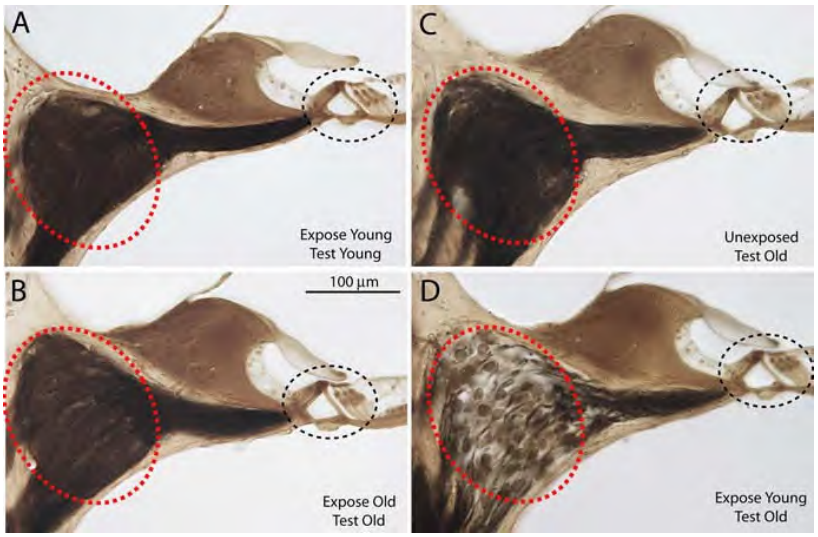


Figure 6. Primary neuronal degeneration was seen in mice that were exposed and allowed to survive for many months. The degeneration, seen as decreased density of spiral ganglion cells (heavy black circles), although inner and outer hair cells (light black circles) are still present, is visible in cases exposed at 6 weeks and aged to 96 weeks (***D***) but not in cases exposed at 96 weeks and evaluated at 98 weeks (***B***) or in unexposed animals tested at 96 weeks (***C***) or in cases exposed at 6 weeks and tested at 8 weeks (***A***). All images are from the upper basal turn. Scale bar in ***B*** applies to ***A–D***.

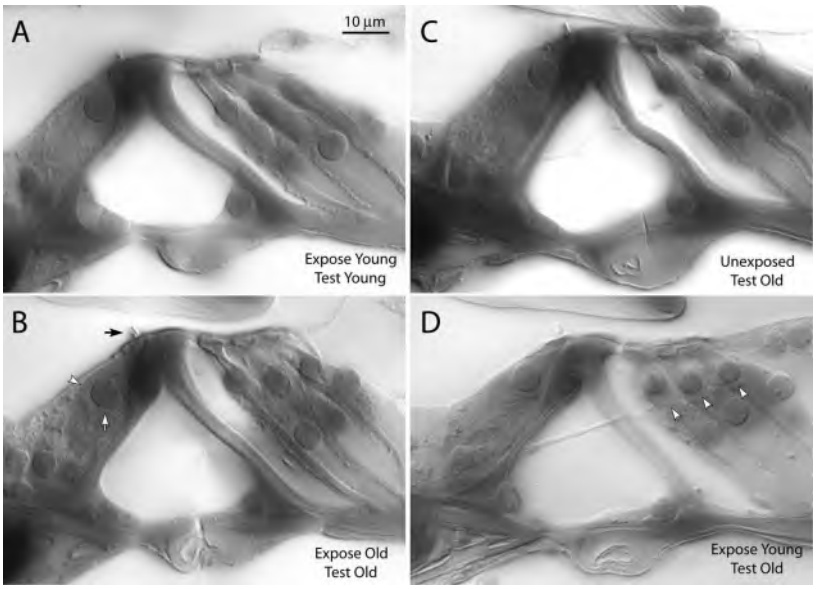


Figure 7. The sensory epithelium appears normal in animals from all exposure groups, even with high-power DIC optics. Images are from the same four cases shown in Figure 6. Each image is focused on an inner hair cell nucleus (e.g., white arrow in ***B***). Stereocilia on inner hair cells are also in focus (e.g., black arrow in ***B***), and, in some cases, the basolateral membrane of the inner hair cell is visible (e.g., white arrowhead in ***B***). Three rows of outer hair cells are seen in all images (e.g., white arrows in ***D***); however, not all rows are in focus. Outer hair cell stereocilia in mouse are generally too small to be visible in this material. The scale bar in ***A*** applies to ***A–D***.

Interactions between noise and age in animal models

Studies of acoustic trauma (Miller et al., 1963) suggest the following: (1) noise-induced threshold shift increases only as long as the noise exposure continues, (2) threshold recovery begins soon after exposure termination, and (3) noise-induced threshold shift asymptotes to permanent and stable levels within 2–4 weeks after exposure. Findings from the present study challenge the universality of these notions. Specifically, we show that noise exposure can lead to threshold shifts that progress for years after the exposure and are associated with primary degeneration of the cochlear nerve. This neural etiology contrasts with the noise-induced hair cell (or stereocilia) damage that underlies the initially measured permanent threshold shifts (Liberman and Dodds, 1984) and contrasts with the aging process in unexposed mice, as shown here and by other studies reporting that cochlear neuronal loss is minimal in unexposed mice, even beyond 2 years of age (Lambert and Schwartz, 1982; Willott et al., 1988; Ohlemiller and Gagnon, 2004).

The present study does not address mechanisms underlying

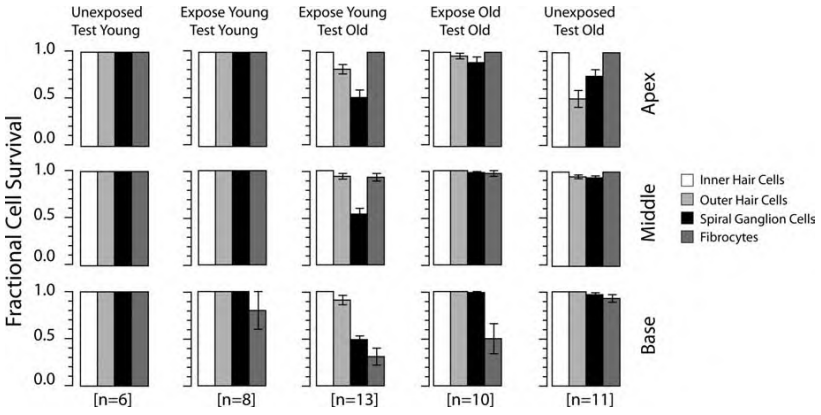


Figure 8. Semiquantitative analysis of cochlear histopathology in groups of exposed and unexposed animals performed by an observer blind to the exposure history and threshold measures. Analysis included estimates of inner and outer hair cell loss, spiral ganglion cell loss, and loss of type IV fibrocytes. Each histogram shows means and SEs or the estimates of fractional cell survival. Estimates were made in three cochlear regions, as indicated, corresponding to the three regions seen in a midcochlear section. The numbers of animals in each group are given under each column letter. "Unexposed Test Young" animals were tested at 7.5 weeks; "Expose Young Test Young" were exposed at 5.5 weeks and tested at 7.5 weeks; "Expose Young Test Old" animals were exposed at 5 weeks and tested at 100 weeks; "Expose Old Test Old" animals were exposed at 124 weeks and tested at 126 weeks; and "Unexposed Test Old" animals were tested at 105 weeks.

the progressive neuropathy; however, it may be important in this regard that the acute response to noise often includes not only temporary threshold shifts but evidence of glutamate excitotoxicity [swelling of afferent nerve terminals under inner hair cells (Pujol et al., 1993)]. Indeed, exposures identical to those used here, delivered at 10 weeks to mice of the same strain, caused temporary threshold shifts that extended across the entire range of frequencies monitored (5.6–45.2 kHz) and obvious swelling of dendrites and cell bodies of cochlear neurons along a broad extent of the cochlear epithelium when evaluated 24 h after exposure (Wang et al., 2002). Although the swelling subsides by 1 week after exposure and synaptic function can return to normal, as evidenced by recovery of ABR thresholds, present results suggest that long-term changes are set in motion that can lead to degeneration on a timescale of months to years.

Progressive threshold deterioration was worst for animals exposed during the "critical period," although some threshold deterioration (and significant associated neuropathy) beyond that expected by aging alone also was seen in animals exposed at older ages and held many months after exposure. This is remarkable because the older animals showed virtually no threshold shift 2 weeks after exposure. Thus, long-term effects of noise exposure can be documented even after an exposure that initially appears to be fully reversible.

Few other studies have followed animals for long postexposure times. However, the two most relevant previous studies, including one in mouse (Li and Borg, 1993) and one in gerbil (Mills et al., 1997), found no evidence for progressive threshold shifts in noise-exposed animals above and beyond those seen in age-matched controls. Histopathology was not evaluated in either case. In the earlier mouse study, CBA/CaJ at 1–12 months were exposed to a 5 min, 120 dB SPL, 2–7 kHz noise band that caused an initial permanent shift of ~20 dB and were held to 23–27 months of age for final ABR testing. In the gerbil study, animals were exposed at 18 months to a 3.5 kHz pure tone for 1 h at 113 dB SPL that caused an initial permanent shift of ~20 dB and were allowed to survive for an additional 18 months before final ABR testing. Apparent discrepancies with current findings may arise from several sources. In the gerbil study, animals were exposed at middle age: in the present study, middle-aged animals held to old age also showed little additional threshold shift. In the mouse study, the short-duration, high-level, low-frequency exposure stimulus may initiate different pathologic processes than those produced here. For example, the loss of spiral ligament fibrocytes seen by 2 weeks after exposure in our animals may not occur after a 5 min exposure such as that used by Li and Borg (1993). Given that spiral ligament fibrocytes may be involved in cytokine signaling pathways and thereby in the stress response of the ear (Adams, 2002), the loss of fibrocytes in our animals may be key in the initiation of long-term neural degeneration.

The magnitude of the ABR shifts in the long-surviving noise-exposed animals is too large to be accounted for by the spiral ganglion cell loss alone. Good thresholds for tones can be maintained after primary neural lesion (Schuknecht, 1993; Parkinson et al., 2001) or neural loss to selective inner hair cell degeneration (Schrott et al., 1989; Wake et al., 1993; Liberman et al., 1997; Hamernik et al., 1998). In addition to the ganglion cells that are frankly missing in these ears, there may be large numbers of unresponsive neurons, perhaps because of degeneration of their peripheral terminals on inner hair cells, as suggested from ultrastructural studies of human temporal bones (Nadol, 1988).

Implications for presbycusis and hearing loss allocation in humans

Aging humans lose threshold sensitivity, especially at high frequencies, and show increasing difficulties discriminating speech in noisy environments. This syndrome of age-related decrements in auditory performance is called presbycusis. For a significant subset of aging individuals, performance on these two functional metrics diverges, with speech intelligibility losses outweighing those expected from threshold sensitivity declines (Pauler et al., 1986). Such performance deficits, together with histologic evidence of primary neural degeneration in some aging ears, have suggested a "neural presbycusis" (Schuknecht, 1993; Schuknecht and Gacek, 1993). Thus, primary neural degeneration of the type seen in the present study could have important consequences in the human, even if the changes in pure tone thresholds are not large.

Current clinical practice and medico-legal procedures often require allocation of noise-induced versus age-related components of hearing losses in aging ears (Dobie, 1992). Methods commonly used to aid such allocations treat these components as though they add simply (with some compression for large shifts) in their contribution to the aggregate hearing loss recorded in a given ear (International Organization for Standardization, 1990, 1999) (see also American College of Occupational Medicine, 1989). This notion has found support in a recent longitudinal study (Lee et al., 2005) reporting that threshold shifts over 3–11.5 year timespans were not significantly different for individuals with and without reported noise-exposure histories. However, two recent studies have yielded data that contradict this view (Gates et al., 2000; Rosenhall, 2003). In the Gates et al. study, ears

with large 3–6 kHz reductions in threshold sensitivity [taken as evidence of previous noise damage (Cooper and Owen, 1976; Kryter, 1985)] demonstrated age-noise interactions resulting in additional hearing loss progression primarily in frequency regions below the original noise-induced threshold shift. Similar changes with age were not seen in ears without these noise notches. This finding was subsequently confirmed by Rosenhall (2003) in analysis of the annual decline of pure tone thresholds in aging men with versus without reported histories of occupational noise exposure. Such observations and those tested more directly here suggest that ears with noise-exposure histories age differently from those without and that the mouse may be a useful animal model in which to systematically study these important issues.

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Systems/Circuits

Aging after Noise Exposure: Acceleration of Cochlear Synaptopathy in "Recovered" Ears

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Cochlear synaptic loss, rather than hair cell death, is the earliest sign of damage in both noise- and age-related hearing impairment (Kujawa and Liberman, 2009; Sergeyenko et al., 2013). Here, we compare cochlear aging after two types of noise exposure: one producing permanent synaptic damage without hair cell loss and another producing neither synaptopathy nor hair cell loss. Adult mice were exposed (8–16 kHz, 100 or 91 dB SPL for 2 h) and then evaluated from 1 h to ~20 months after exposure. Cochlear function was assessed via distortion product otoacoustic emissions and auditory brainstem responses (ABRs). Cochlear whole mounts and plastic sections were studied to quantify hair cells, cochlear neurons, and the synapses connecting them. The synaptopathic noise (100 dB) caused 35–50 dB threshold shifts at 24 h. By 2 weeks, thresholds had recovered, but synaptic counts and ABR amplitudes at high frequencies were reduced by up to ~45%. As exposed animals aged, synaptopathy was exacerbated compared with controls and spread to lower frequencies. Proportional ganglion cell losses followed. Threshold shifts first appeared >1 year after exposure and, by ~20 months, were up to 18 dB greater in the synaptopathic noise group. Outer hair cell losses were exacerbated in the same time frame (~10% at 32 kHz). In contrast, the 91 dB exposure, producing transient threshold shift without acute synaptopathy, showed no acceleration of synaptic loss or cochlear dysfunction as animals aged, at least to ~1 year after exposure. Therefore, interactions between noise and aging may require an acute synaptopathy, but a single synaptopathic exposure can accelerate cochlear aging.

Key words: age-related hearing loss; auditory nerve; cochlear neuropathy; cochlear synaptopathy; noise-induced hearing loss; temporary threshold shift

Introduction

Noise exposure and aging are two common causes of hearing loss in humans, often occurring in the same ears. Traditionally, the influence of noise exposure on the ear and hearing has been viewed as time limited: exposure produces "hearing loss" (threshold elevations) and cochlear injury, with effects that appear largest at early postexposure times. Varying degrees of structural and functional recovery can be seen in the hours to weeks after exposure. This period of fairly rapid recovery is followed by one of relative stability, giving the impression that noise, once it stops, produces no progressive or delayed consequences as exposed individuals age (Institute of Medicine, 2005; American College of Occupational and Environmental Medicine, 2012).

Much of the evidence cited in support of this view is based on audiometric thresholds, which are generally good at reflecting damage to hair cells, but not damage to the sensory neurons innervating them, particularly when the neuropathy is subtotal or diffuse (Schuknecht and Woellner, 1955; Liberman et al., 1997; Kujawa and Liberman, 2009; Lobarinas et al., 2013; Sergeyenko et al., 2013; Bourien et al., 2014). Our recent work has shown that both aging and noise exposure have insidious consequences not revealed by standard threshold metrics. With respect to auditory aging, early events include diffuse loss of synapses between inner hair cells (IHCs) and cochlear nerve fibers throughout the cochlea (Sergeyenko et al., 2013). This synaptopathy is progressive, is reflected proportionately in declining neural response amplitudes, and is evident well before age-related reductions in threshold sensitivity or hair cell numbers. Similarly, noise exposure causing robust but reversible changes in threshold sensitivity and no hair cell loss can nevertheless destroy cochlear synapses and reduce neural responses. These noise-induced synaptopathies are visible within 24 h after exposure (Kujawa and Liberman, 2009; Lin et al., 2011). Although the noise-induced threshold elevations can recover by 2 weeks after exposure, IHCs remain partially denervated and neural response amplitudes are permanently reduced for cochlear frequencies showing maximum acute threshold shift, that is, those from basal (high-frequency) regions of this mechanically tuned sensory organ. Cochlear places apical to the region of acute threshold shift appear unaffected in the same postexposure timeframe.

Over the course of a human lifetime, noise exposures producing reversible threshold shifts are common from both occupational and recreational sources (Rabinowitz, 2012). Long-term or

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delayed effects of such exposure on the aging ear are poorly understood and generally viewed as insignificant. Here, in a mouse model, we examine the extent to which noise that produces reversible shifts in threshold sensitivity but permanent synaptic injury also influences subsequent cochlear aging. We contrast these outcomes with those arising after an exposure that also produces a robust temporary threshold shift but in the short term produces neither synaptic nor hair cell loss. We show that a single episode of synaptopathic noise early in life can exaggerate dramatically the loss of cochlear synapses and cochlear neurons that otherwise occurs with age and can produce delayed loss of threshold sensitivity and outer hair cells (OHCs). These findings question long-held assumptions about the stability of noise-induced cochlear injury and have important implications for public health.

Materials and Methods

Animals and groups. CBA/CaJ mice (males) were used in these studies. Animals were born and reared in our colony from inbred breeders obtained from The Jackson Laboratory. We have described the colony and the acoustic environment in which mice are raised previously (Sergeyenko et al., 2013). Here, mice entered the experimental protocol at 16 weeks of age and were assigned to one of the following groups. Group 1 (synaptopathic exposure) animals received our previously characterized, 8–16 kHz, 100 dB SPL, 2 h exposure and were held for varying postexposure times from 1 h to 20 months before physiologic evaluation and retrieval of cochlear tissues. Group 2 (nonsynaptopathic exposure) animals received an exposure of identical frequency content and duration, but reduced level (91 dB SPL) that produced no acute synaptic loss; after exposure, they were tested and processed as for Group 1. Group 2b animals received the same exposure as for Group 2, but delivered for 8 h; this group was studied at short postexposure times only to assess differences in acute cochlear synaptopathy. Group 3 (age-only controls) were unexposed, age-matched animals that were treated identically except for the noise and were held with exposed cage mates until final testing and processing at ages from 16 to 104 weeks, encompassing the range of postexposure holding times. All procedures were approved by the institutional animal care and use committee of the Massachusetts Eye and Ear Infirmary.

Acoustic overexposures. Awake mice were placed unrestrained in a subdivided cage with one mouse per division. Noise stimuli were created by a waveform generator (model WGI; Tucker-Davis Technologies), bandpass filtered (8–16 kHz, >60 dB/octave slope; Frequency Devices), amplified (D-75 power amplifier; Crown Audio) and delivered (compression driver; JBL) via an exponential horn projecting into a reverberant tabletop exposure chamber with the subdivided cage suspended directly below. Before each exposure, noise levels were calibrated to one of the target SPLs (100 or 91 dB).

Physiology: distortion product otoacoustic emissions and auditory brainstem responses. Physiologic tests were conducted on anesthetized mice (ketamine 100 mg/kg and xylazine 10 mg/kg, i.p.) in an acoustically and electrically shielded, heated chamber. All testing was conducted using a National Instruments PXI-based system with 24-bit input/output boards controlled by a custom LabView-based software program. Sound sources consisted of two miniature dynamic earphones (CDMF15008-03A; CUI). A condenser microphone (FG-23329-PO7; Knowles) coupled to a probe tube measured sound pressure in the ear canal. A small V-shaped incision was made in the cartilaginous portion of the external ear canal to facilitate viewing and confirmation of a healthy tympanic membrane and to optimize placement of the acoustic system.

Auditory brainstem responses (ABRs) and distortion product otoacoustic emissions (DPOAEs) were recorded for all animals. Tone burst ABRs (0.5 ms rise-fall, 5 ms duration, 30/s, alternating polarity) were measured as functions of increasing stimulus level (5 dB steps) at log-spaced frequencies from 5.6 to 45.2 kHz using subdermal needle electrodes at the vertex and ventrolateral to the pinna, with a ground electrode at the base of the tail. Responses were amplified (10,000×), filtered (0.3–3 kHz), and averaged (1024 samples/level). Threshold was determined as the lowest level at which a repeatable Wave 1 could be identified. Peak-to-peak Wave 1 amplitude was determined using an offline analysis program. DPOAEs were recorded at $2f_1$-f_2 in response to two primary tones, f_1 and f_2, with f_2 equal to the frequencies used in ABR testing, $f_2/f_1 = 1.2$ and L2 = L1–10 dB, both incremented together in 5 dB steps. At each level combination, the amplitudes of the DPOAE responses at $2f_1$-f_2 were captured from ear canal pressure measurements, and, after spectral and waveform averaging, were analyzed, offline, as response-growth functions. Iso-DPOAE contours were interpolated from the growth functions and used to determine the f_2 level required to elicit a DPOAE of −5 dB SPL at each frequency, which was defined as threshold.

Histology. Anesthetized mice were transcardially perfused with 4% paraformaldehyde in 0.1 M phosphate buffer, followed by an additional intralabyrinthine perfusion through the oval and round windows of both cochleas. One cochlea was used for immunostained epithelial whole mounts and the other for osmium-stained, plastic-embedded sections. Cochleas destined for immunostaining underwent an additional 1 h postfixation in 4% paraformaldehyde and were then decalcified in 0.12 M EDTA for up to 48 h. Microdissected pieces were immunostained with antibodies to the following: (1) C-terminal binding protein 2 (mouse anti-CtBP2; BD Biosciences, used at 1:200), (2) myosin-VIIa (rabbit anti-myosin-VIIa; Proteus Biosciences; used at 1:200), and (3) GluA2 (mouse anti-glutamate receptor 2; Millipore; used at 1:2000) with appropriate secondary antibodies coupled to Alexa Fluors in the red, blue, and green channels. Cochleas used for spiral ganglion analysis were postfixed in 2% formaldehyde and 2% glutaraldehyde in 0.1 M phosphate buffer overnight, decalcified in 0.12 M EDTA for several days, rinsed in phosphate buffer, and osmicated (1% osmium tetroxide) for 45 min. Tissues were then rinsed (0.1 M phosphate buffer and ddH_2O), dehydrated, and embedded in Araldite in a stereotyped orientation for serial sectioning (10 μm sections, parallel to the modiolus) using a Leica RM2255 microtome. Sections were mounted in Permount on microscope slides for quantification.

Cochlear mapping and hair cell and synaptic counts. Immunostained cochlear pieces were measured and a cochlear frequency map was computed (Müller et al., 2005) to associate structures to relevant frequency regions using a custom plug-in to ImageJ. Confocal *z*-stacks of the 5.6, 11.3, 22.6, and 32 kHz areas were collected using a Leica TCS SP2 or SP5. Two adjacent stacks were obtained (78 μm of cochlear length per stack) at each target frequency, spanning the cuticular plate to the synaptic pole of ~10 hair cells (in 0.25 μm *z*-steps). Images were collected in a 1024 × 512 raster using a high-resolution, oil-immersion objective (SP2: 100×, numerical aperture 1.4; SP5: 63×, numerical aperture 1.3) and digital zoom (SP2: 2×; SP5: 3.17×). Images were loaded into an image-processing software platform (Amira; VISAGE Imaging), where IHCs were quantified based on their CtBP2-stained nuclei and synaptic ribbons (with or without paired glutamate receptor patches or terminals) could be counted using 3D representations of each confocal *z*-stack. These synaptic associations were determined using custom software that calculated and displayed the *x–y* projection of the voxel space within 1 μm of each ribbon's center (Liberman et al., 2011).

OHCs were identified in the same epithelial regions using a Nikon Eclipse E800 with a 40×, numerical aperture 0.95 objective. OHCs were counted separately for each OHC row within a 290 μm viewing field. OHC ribbons were counted in subsets of exposed and unexposed animals, spanning the range of ages studied.

Spiral ganglion cell quantification. Spiral ganglion neurons were quantified at four corresponding cochlear regions: 5.6, 11.3, 22.6, and 32 kHz. One section was analyzed in each cochlear region, selected to be precisely in the middle of that half-turn of the cochlear spiral. Rosenthal's canal of this section was live-imaged using DIC optics on a Nikon E600 microscope with a digital camera interfaced to Neurolucida software (version 11.0; MBF Bioscience). At 20×, the continuous tracing function was used to create a closed contour (outline) of the area of Rosenthal's canal. At 40×, while rolling the focus to view the entire thickness of the section, the software was used to place a marker at the *x–y* position of each visible ganglion cell nucleolus. The data file (consisting of the outline of each area and the markers within it) was then opened in Neurolucida Explorer

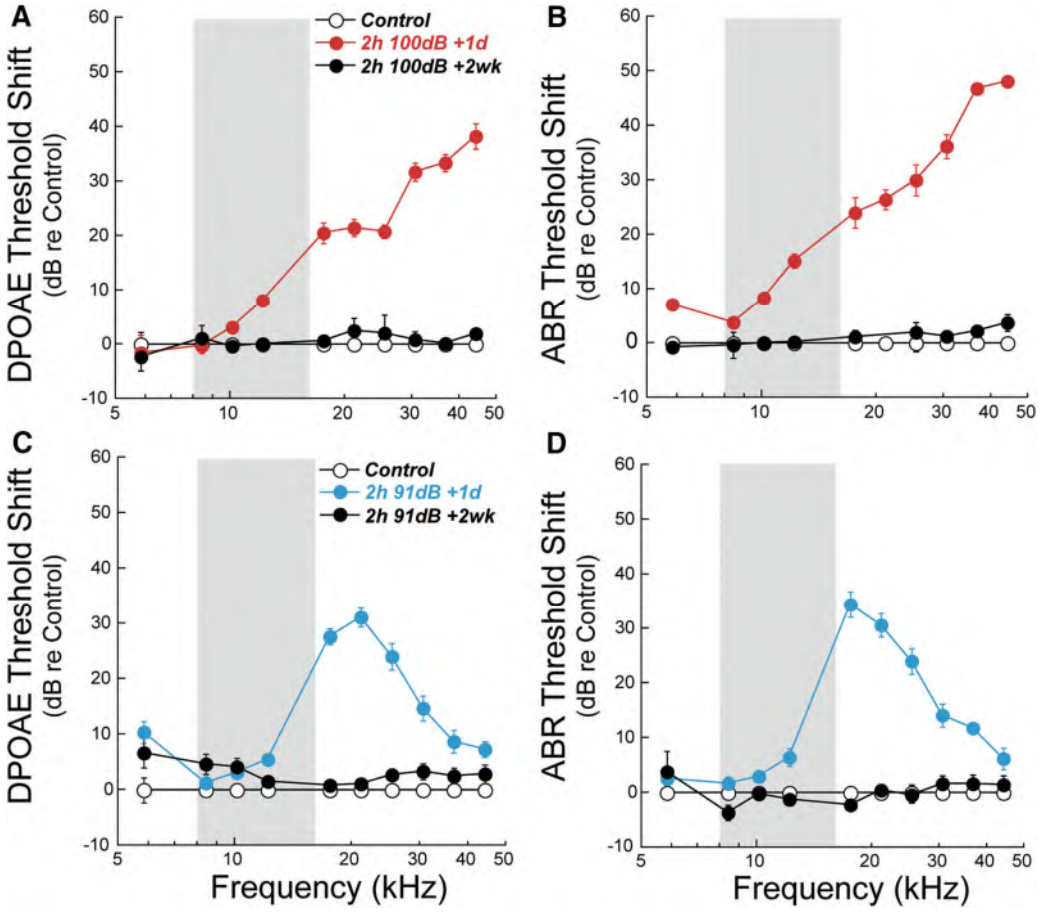

Figure 1. Noise-induced threshold shifts. In 16-week-CBA/CaJ mice, exposure to an octave-band noise (8–16 kHz) at 100 dB SPL for 2 h produces large (40–50 dB at 24 h), but temporary, threshold shifts in both DPOAEs (***A***) and ABRs (***B***). The same noise band at 91 dB SPL for 2 h produces ~30 dB TTS at 24 h after exposure, more restricted in frequency than after 100 dB noise, with maximum damage shifted to lower frequencies (***C***, ***D***). For both exposures, DPOAE and ABR Wave 1 thresholds recover to control levels by 2 weeks. Data are means ± SE. Group sizes were as follows: 16 week unexposed (15); exposed 100 dB, 2 h - held 24 h (14), held 2 week (15); exposed 91 dB, 2 h - held 24 h (11), held 2 week (10). The gray bar denotes the pass band of the noise-exposure stimulus.

(MBF Bioscience), the contour analysis function of which yielded the area of the outlined region in square micrometers. Density is expressed as SGNs/10,000 μm^2.

Results

Patterns of acute threshold shift and initial recovery

Recent work suggests that cochlear synapses, not sensory cells, are most vulnerable to acoustic injury and aging (Kujawa and Liberman, 2009; Sergeyenko et al., 2013). Young adult ears receiving exposures producing only temporary threshold shift (TTS) and no hair cell loss can show an immediate and permanent loss of synapses between cochlear nerve terminals and IHCs. Here, we investigated whether such noise exposures can nevertheless influence the vulnerability of the ear to subsequent age-related changes. For comparison, we evaluated a synaptopathic exposure producing immediate and irreversible loss of cochlear nerve synapses and a less intense exposure that did not produce any immediate synaptopathy (or hair cell loss), although it also produced a significant TTS.

To produce acute synaptopathy, we presented an octave-band noise in the middle of the mouse hearing range (8–16 kHz) at 100 dB SPL for 2 h (Kujawa and Liberman, 2009). In the present series, this exposure produced maximum threshold shifts of 35–50 dB when measured in DPOAEs and ABRs at 24 h after exposure (Fig. 1*A*,*B*). Acute shifts increased with increasing frequency above the exposure band. The shifts were slightly greater when measured in ABRs than in DPOAEs and they recovered by 2 weeks after exposure.

For comparison, we wanted a group that experienced the stress of a TTS-producing acoustic overexposure but at a level low enough that neither hair cell loss nor cochlear nerve synaptopathy was observed in the acute postexposure period. Using the same noise band and exposure duration, we progressively halved its energy (reducing level in 3 dB steps) until we identified a level (91 dB SPL) that produced no acute loss of synapses (see below). This "nonsynaptopathic" exposure produced maximum threshold shifts of 30–35 dB at 24 h after exposure (Fig. 1*C*,*D*). Threshold shifts from the lower-level exposure were more restricted in frequency and peaked at a lower frequency (~20–22 kHz) than for the same noise band presented at the higher level. Thresholds measured by both ABRs and DPOAEs also recovered to baseline values by 2 weeks after exposure.

Patterns of acute and progressive synaptic loss and spiral ganglion cell loss

All of the myelinated sensory fibers in the cochlear nerve contact exclusively the IHCs, as schematized in Figure 2*A* (Spoendlin,

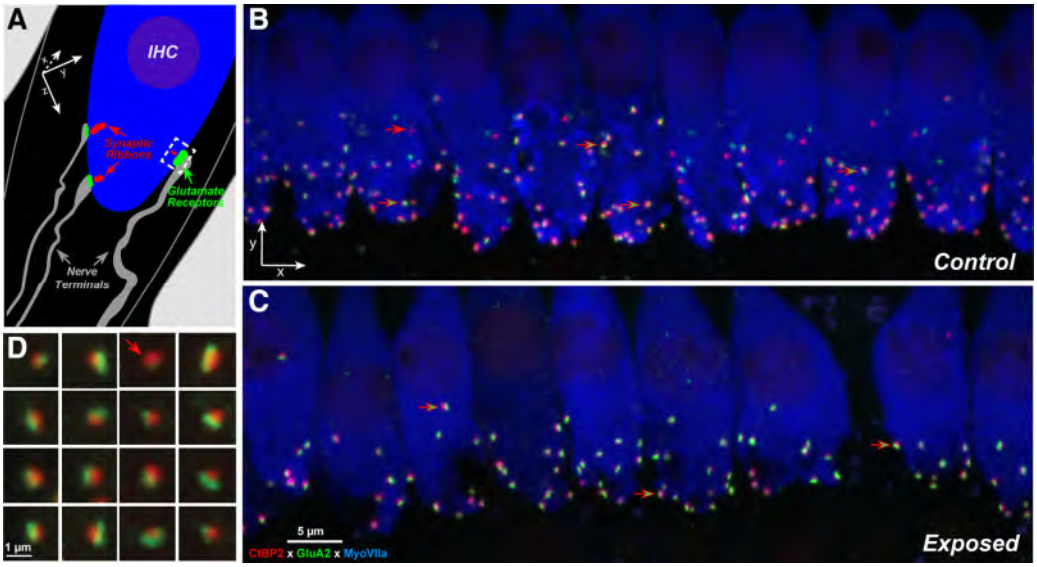

Figure 2. Confocal imaging and quantification of IHC synapses. ***A***, Schematic of the IHC area showing the presynaptic and postsynaptic elements we immunostain to assess synaptopathy. The white box indicates the region displayed in each thumbnail image in ***D***. ***B***, ***C***, Confocal images of IHC synapses from the 32 kHz region of an unexposed, 16-week-old control (***B***) and an exposed (***C***; 2 weeks after 100 dB, 2 h exposure) cochlea immunolabeled for presynaptic ribbons (CtBP2-red), postsynaptic receptor patches (GluA2-green), and IHCs (mysoin VIIa, blue). In unexposed ears, whether young or old (16 week shown in ***B***), virtually all immunostained ribbons are paired with a glutamate receptor patch (red-fill green arrows); in exposed ears, some "orphan" ribbons (red arrows in ***C*** and ***D***) are unpaired with postsynaptic puncta. ***D***, High-power reprojections in the *z*–*y* plane were used to quantify the numbers of orphan ribbons.

1972). The normal synapse between an IHC and a cochlear nerve terminal comprises a presynaptic ribbon with its associated halo of neurotransmitter-containing vesicles (Liberman, 1980; Liberman et al., 1990) and a postsynaptic active zone with glutamate receptors for the released neurotransmitter (Matsubara et al., 1996; Ruel et al., 2007; Meyer et al., 2009; Grant et al., 2010). To identify and count synapses on IHCs, we used antibodies to CtBP2, a prominent component of the presynaptic ribbon (Khimich et al., 2005), and to GluA2 subunits to identify postsynaptic receptor patches (Matsubara et al., 1996). Synapses were defined as juxtaposed pairs of CtBP2- and GluA2-positive puncta, as schematized in Figure 2*A*. Maximum confocal projections from unexposed (Fig. 2*B*) and exposed (Fig. 2*C*) IHCs reveal the loss of synapses seen immediately after exposure. To allow unambiguous identification of synapses (i.e., ribbons with closely apposed receptor patches) versus "orphan" ribbons or receptor patches, we used custom software that displays the voxel space from the confocal *z*-stack within a small cube centered on each immunostained ribbon (or receptor patch), as shown in Figure 2*D*.

In the present study, synapses were counted in four cochlear regions, including zones of minimal (5.6 and 11.3 kHz) and maximal (22.6 and 32 kHz) acute threshold elevation from the TTS-producing noise. Synapse numbers declined gradually with age in all four regions (Fig. 3*A*–*D*), as reported previously (Sergeyenko et al., 2013). Losses reached 15–25%, depending on cochlear frequency, by 104 weeks of age. Immediately after the 2 h, 91 dB exposure, there were no synaptic losses in any cochlear regions (Fig. 3*A*–*D*). Therefore, the 91 dB exposure is initially nonsynaptopathic, although threshold shifts were as high as 40 dB when measured 24 h after exposure (Fig. 1). In contrast, ears exposed for 2 h at 100 dB SPL showed an immediate (~35–55% within 1 h) reduction in synaptic counts at the two high-frequency locations (Fig. 3*C*,*D*), as reported previously for the same exposure (Kujawa and Liberman, 2009).

In addition to this loss of synapses (paired ribbon-receptor puncta), we observed that ribbon counts per se were higher than synaptic counts when assessed 1 h after 100 dB, but not 91 dB, exposure. In normal ears, there is a nearly one-to-one pairing between ribbons and glutamate receptor patches (Figs. 2*B*, 4*A*–*C*). In the 100 dB-exposed ears, ~26% of the ribbons that remained in the maximum damage region (Fig. 4*C* vs *A*,*B*) were "orphans" at 1 h after exposure. By 24 h, this number had fallen to ~8% and, by 2 weeks, virtually all remaining ribbons were once again paired with glutamate receptor patches, as in the control ears. This change in the number of GluA2 puncta could reflect a transient internalization of surface glutamate receptors, as documented previously in response to glutamate agonists *in vitro* or noise *in vivo* (Chen et al., 2007). This reversible downregulation of surface AMPA receptors may serve a protective function (Chen et al., 2007, 2009) by modulating synaptic strength.

In prior work, we followed the progression of synaptopathy after the 100 dB exposure for 8 weeks and saw no signs of synaptic recovery in the damaged regions (Kujawa and Liberman, 2009). Here, we followed the postexposure ears for up to 88 weeks after exposure and again saw no signs of synaptic recovery (Fig. 3). Indeed, the trend was toward ongoing synaptic degeneration. When this trend in aging 100 dB-exposed ears is compared with the age-related synaptic decline in control ears, key differences are evident. First, despite an initial absence of apical synaptic loss in the exposed mice, the degeneration spreads apically as animals age, outpacing declines in control ears at 16 weeks after exposure and beyond (Fig. 3*A*,*B*). Second, cochlear regions with large acute losses (Fig. 3*C*,*D*) show continued age-related declines, but at a slower pace (fewer synapses lost per year) than age-only controls and also at a slower pace than in cochlear regions with minimal acute losses (Fig. 3*A*,*B*). This deceleration of ongoing synaptic loss is consistent with the idea that a subset of cochlear nerve terminals is more vulnerable to noise and to aging (Schmiedt et al., 1996; Furman et al., 2013) and that many of

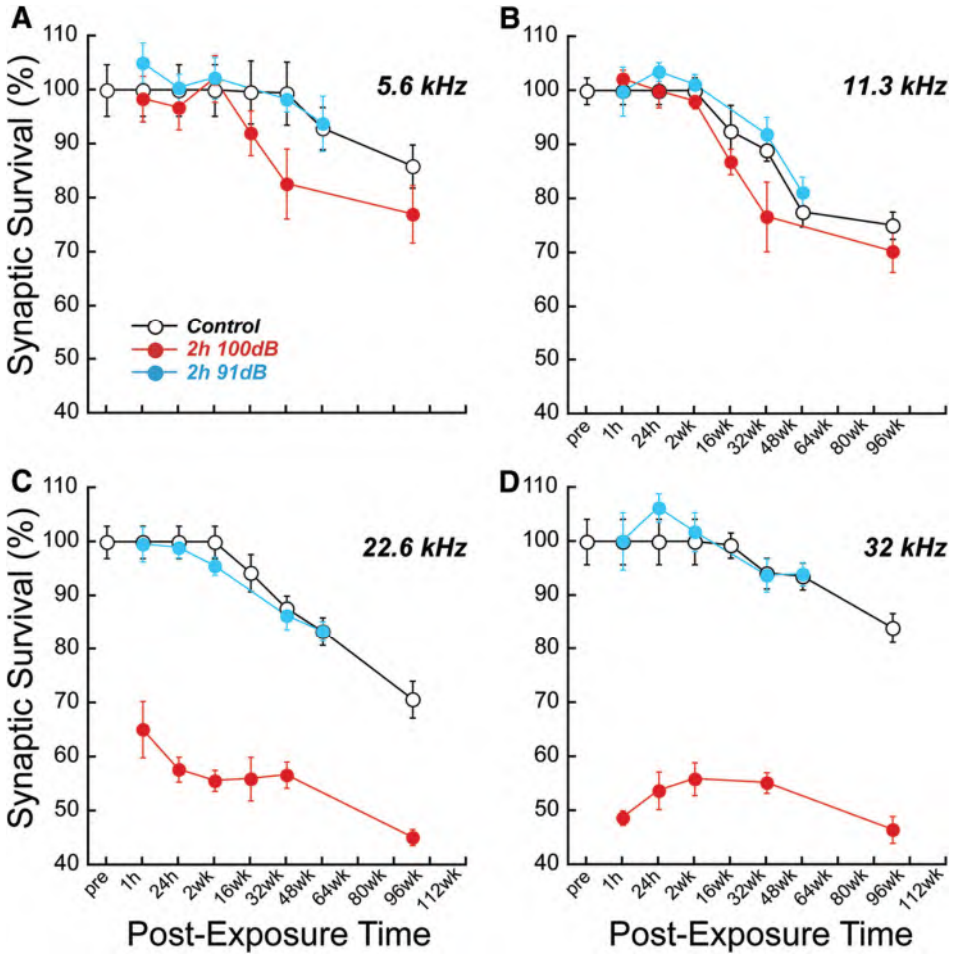

Figure 3. Age- and noise-induced synapse loss. In unexposed ears, synapse counts decline gradually with age (open symbols, ***A***–***D***). Synaptopathic noise (red symbols, 100 dB, 2 h) immediately produces 35% synapse loss in basal cochlear regions (***C***, ***D***) without loss in regions of minimum TTS (***A***, ***B***). With advancing age, losses spread apically, exceeding those in age-matched controls. There is no acute synapse loss for the 91 dB exposure (teal symbols, ***A***–***D***) and no obvious interaction between noise and aging. Means (± SE) are normalized to 16 week, unexposed values. Group sizes were as follows: unexposed-16 week (15), 32 week (5), 64 week (7), 80 week (9), 104 week (6); exposed 100 dB, 2 h- held 1 h (12), 24 h (14), 2 week (15), 16 week (7), 48 week (5), 88 week (6); exposed 91 dB, 2 h- held 1 h (5), 24 h (11), 2 week (10), 48 week (5), 64 week (6).

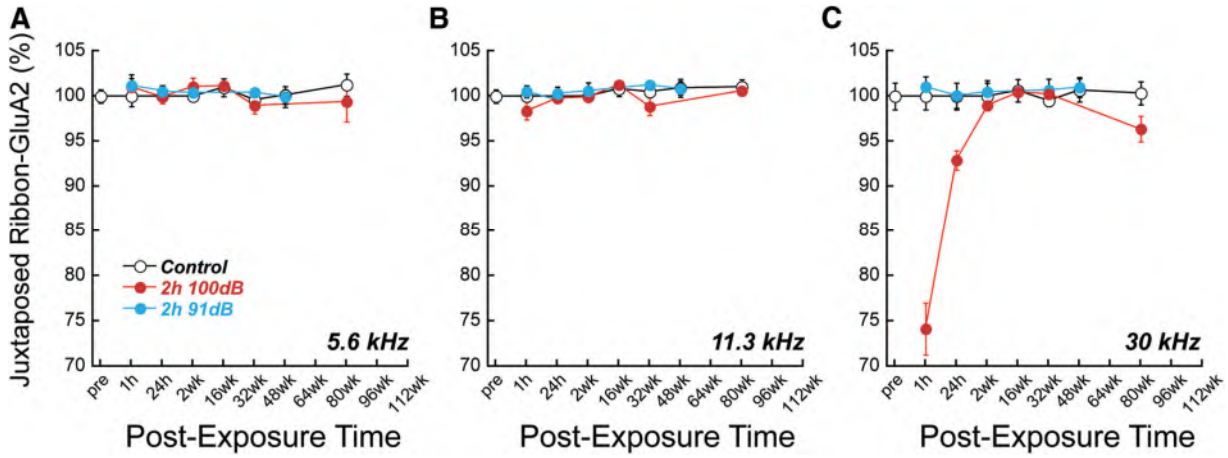

Figure 4. Transient postnoise reductions in GluA2-positive puncta. When quantified 1 h after synaptopathic noise, counts of GluA2-immunostained glutamate receptor patches are reduced by >25% in the maximum damage region (cf. ***C*** vs ***A***, ***B***). By 2 weeks after exposure, virtually all remaining ribbons again display colocalized receptor patches, as in control ears. Counts in ears receiving nonsynaptopathic exposure did not display similar, dynamic changes. Group sizes are provided in the Figure 3 legend.

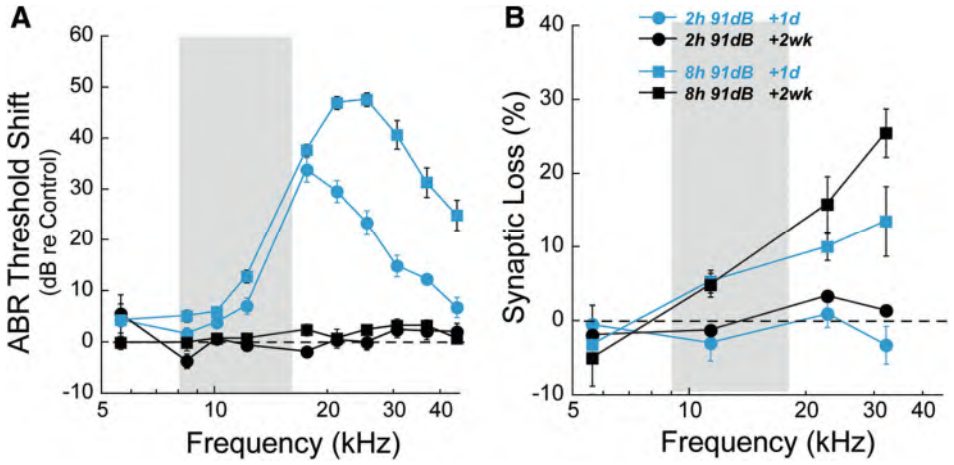

Figure 5. Nonsynaptopathic exposure becomes synaptopathic with longer duration. ABR threshold shift (***A***) and synapse loss (***B***) compared with 16 week controls are shown for nonsynaptopathic (91 dB, 2 h) and synaptopathic (91 dB, 8 h) exposures at 1 d and 2 weeks after exposure. For both metrics, longer exposure resulted in increased magnitude and basalward shift of maximum injury. Although thresholds for both exposures recover, synapse loss is persistent and displays some early progression in the highest frequency regions. Key in ***B*** applies to both panels. Group sizes were as follows: 16 week unexposed (15); exposed 91 dB, 2 h - held 24 h (11), held 2 week (10); exposed 91 dB, 8 h - held 24 h (8), held 2 week (11).

these were lost acutely with the 100 dB exposure, limiting further change with age. OHC ribbon counts in the same ears were essentially unaffected: for surviving OHCs, ribbon losses were small and similar (±3% of 16 week controls at 32 kHz) in 104-week-old ears with or without 100 dB exposure at 16 weeks (Kujawa and Liberman, 2009; Sergeyenko et al., 2013).

By design, the 2 h, 91 dB exposure produced no acute loss of synapses (Fig. 3*A–D*); however, when the same exposure was instead delivered for an 8 h period, the acute consequences of the noise were magnified and shifted basally (Fig. 5*A*, *B*). The longer exposure caused greater TTS at high frequencies, but shifts at 18 kHz and below were virtually identical for the 2 and 8 h exposures (Fig. 5*A*). There also was evidence of acute synaptopathy after the 8 h exposure; synaptic loss increased with cochlear frequency and appeared progressive with postexposure time, with up to ~25% loss in the damage region (Fig. 5*B*) over the 2 week period of monitoring. These findings suggest that basal cochlear injury may be important to the generation of progressive synaptopathies (see Discussion).

We also counted spiral ganglion cells, the cell bodies of cochlear nerve fibers. Figure 6 shows images from young (16 weeks; Fig. 6*A*) and old (104 weeks; Fig. 6*B*) unexposed ears compared with an ear exposed (100 dB for 2 h) at 16 weeks and held to the same 104 week chronological age (Fig. 6*C*). Cell counts, obtained in the same cochlear regions as for synapse counts, revealed proportional losses. Figure 6 shows data for 11.3 kHz, in a region of minimal age-related and noise-induced threshold elevation (Fig. 6*D*) and 32 kHz in the region of maximal shifts for both (Fig. 6*E*). As ears aged with or without prior noise exposure, synapse loss was an excellent predictor of the ultimate loss of spiral ganglion cells. Ganglion cell losses from aging alone were modest, reaching ~20% by 104 weeks in both cochlear locations. For ears with synaptopathic exposure, subsequent losses began earlier and ultimately exceeded those for age-only controls: by almost 25% at 11.3 kHz (Fig. 6*D*) and by almost 40% at 32 kHz (Fig. 6*E*), as shown for synapse losses in the two groups (Fig. 3*B*, *D*). Ganglion cell counts in the nonsynaptopathic group were not different from those of unexposed, age-matched controls, at least to 64 weeks of age, consistent with the similarity in age-related synaptic losses in these two groups (Fig. 3).

Patterns of acute and progressive hair cell loss

Consistent with our previous report (Sergeyenko et al., 2013), OHC losses in unexposed aging ears appeared relatively late, between 1 and 2 years (Fig. 6). At 104 weeks, losses in the apical-most region (5.6 kHz; Fig. 7*A*) were 60%. At middle- to high-frequency places (Fig. 7*B–D*), losses were <10%, although in the extreme base (not sampled here), losses also rose to ~50% over the same span of ages (Spongr et al., 1997). Losses at all ages were similar across all OHC rows.

OHCs were not lost acutely after exposure to either the 91 dB or the 100 dB noise, but at 100 dB, there was a slight exacerbation of OHC death at the oldest survival (Fig. 7*A–D*). These differences from age-matched controls were statistically significant at 32 kHz only ($p < 0.01$, Bonferroni *post hoc* pairwise comparisons). The loss was greatest for row 1 hair cells, the same pattern seen in the acute response to acoustic injuries that cause PTS (Robertson and Johnstone, 1980; Saunders et al., 1991). IHC loss was minimal (~5%) at all ages in all cochlear regions and was not exaggerated by prior noise, at least over the range of postexposure times sampled here (Fig. 7*A–D*).

Age-related decline of cochlear function in noise-exposed and control ears

Noise exposure producing TTS and acute loss of IHC synapses has immediate and delayed effects on cochlear function. Synaptic loss is reflected in permanently reduced suprathreshold amplitudes of cochlear neural responses, because communication between hair cells and cochlear nerve fibers is permanently interrupted. Suprathreshold growth of response amplitude was assessed at all postexposure times and frequencies of threshold monitoring by both DPOAEs and ABRs. Figure 8 compares responses from age-only ears versus ears that were exposed and then aged. We focus here on the maximum damage region for the synaptopathic, 2 h 100 dB exposure (32 kHz; Fig. 8*A*, *B*) and for the nonsynaptopathic, 2 h 91 dB exposure (22 kHz; Fig. 8*C*,*D*). Several key patterns emerged: In age-only ears (open symbols) DPOAEs changed little with time; amplitude-level functions (Fig. 8*A*, *C*) are largely overlapping except at 32 kHz where 104 week animals showed a ~15 dB rightward shift, suggesting OHC dysfunction. In comparison, amplitudes of ABR Wave 1 (Fig. 8*B*, *D*)

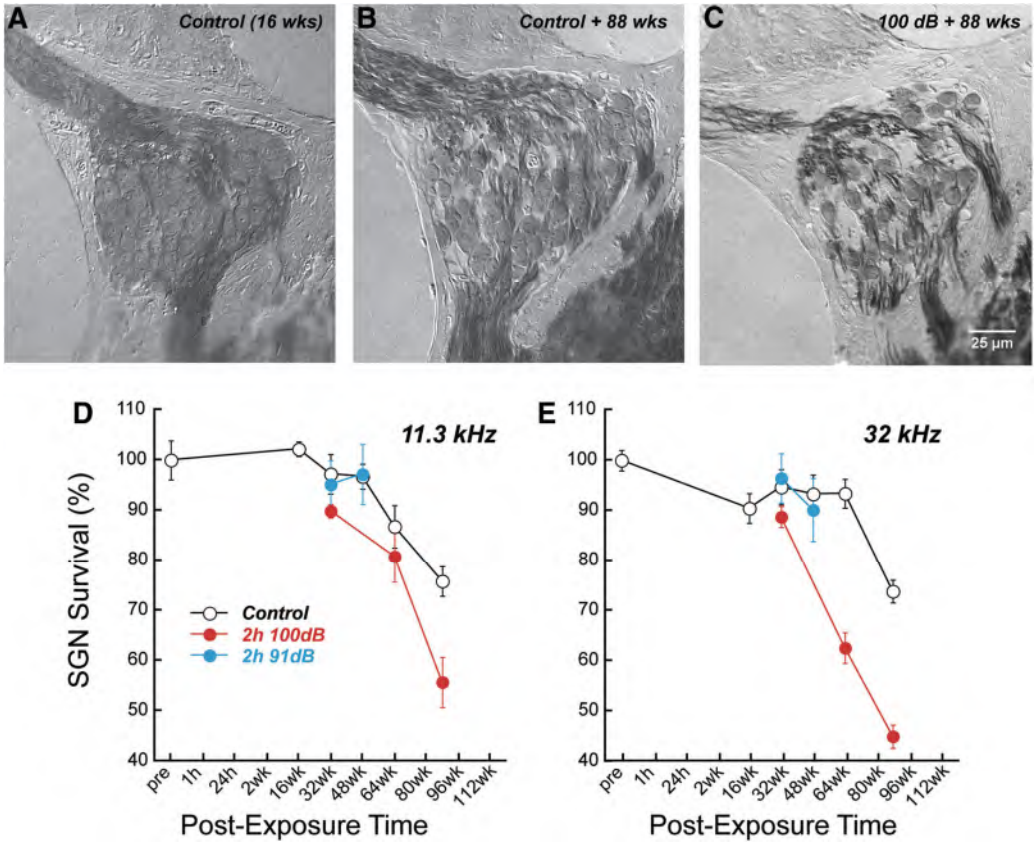

Figure 6. Synaptopathic noise exposure exacerbates spiral ganglion cell loss as animals age after noise. Representative cochlear sections from the 32 kHz region of control (***A***:16 weeks chronological age, unexposed); control + 88 weeks (***B***:104 weeks chronological age, unexposed); and 100 dB + 88 weeks (***C***:exposed at 16 weeks, held 88 weeks to 104 weeks chronological age) showing exaggerated loss of spiral ganglion cells in ears aged after exposure to synaptopathic noise. Scale bar in ***C*** applies to all SGN images. Cell counts in groups (means ± SE, group sizes are provided in Fig. 3 legend) with and without prior noise are displayed at two frequencies: 11.3 kHz (***D***) and 32 kHz (***E***).

declined progressively, beginning well before OHC loss and greatly exceeding changes in the DPOAEs. Again, changes were largest at the higher frequency.

After exposure, response amplitudes for both metrics were acutely reduced in the TTS region (filled red symbols in Fig. 8). DPOAE amplitudes recovered to control levels by 2 weeks for both exposures (Fig. 8*A*,*C*). Synaptopathic, but not nonsynaptopathic, exposure caused permanent reductions in ABR Wave 1, the summed activity of cochlear nerve fibers (Fig. 8*B* vs *D*). As animals aged after synaptopathic exposure, ABR amplitude reductions were exaggerated compared with age-only controls (compare filled vs open symbols in Fig. 8*B*). At the oldest age, exaggerated declines also are evident in the DPOAEs (Fig. 8*A*), suggesting progressive injury to OHC function. For the nonsynaptopathic exposure, neural amplitude reductions were not exaggerated compared with age-only ears (overlapping open and filled symbols), at least to 48 weeks after exposure (Fig. 8*D*).

In contrast to the early appearance of age-related synaptic loss (Fig. 3) and Wave 1 amplitude decline (Fig. 8), age-related onset of threshold elevation occurs relatively late in CBA/CaJ mice. Here, age-only controls demonstrated small, mid- to high-frequency threshold shifts through 104 weeks of age (data not shown; Sergeyenko et al., 2013). After noise-induced TTS, once thresholds had recovered to control levels (2 weeks after exposure), they remained relatively stable compared with controls for nearly one year. By the longest postexposure time (88 weeks), animals receiving the 100 dB noise showed slightly larger threshold shifts, greater by ABRs (~10–18 dB) than DPOAEs (~5–10 dB), as shown in Figure 9 for data at 32 kHz. Group differences reached significance at 11.3, 22.6, and 32 kHz for both DPOAEs and ABRs ($p < 0.01$, Bonferroni *post hoc* pairwise comparisons). Thresholds for animals receiving the nonsynaptopathic exposure were not different from controls, at least to 64 weeks (data not shown).

Discussion

Synaptopathic versus nonsynaptopathic exposures and the relation to TTS magnitude

Hair cells have long been considered to be the most vulnerable elements in the inner ear and the primary targets of damage after acoustic overexposure (Bohne and Harding, 2000). However, recent work shows that, in both noise-exposed and aging ears, synapses between IHCs and cochlear nerve terminals degenerate long before the hair cells themselves (Kujawa and Liberman, 2009; Sergeyenko et al., 2013). In ears that age without prior acoustic injury, the diffuse loss of afferent synapses on IHCs is gradually progressive throughout life and throughout the cochlea (Sergeyenko et al., 2013). After noise, the loss is sudden and most severe in the cochlear frequency region where the acute threshold shift is maximal. In either case, loss of a cochlear nerve fiber's sole synaptic connection to the sensory cell renders it unresponsive to sound. However, thresholds, long considered the gold standard met-

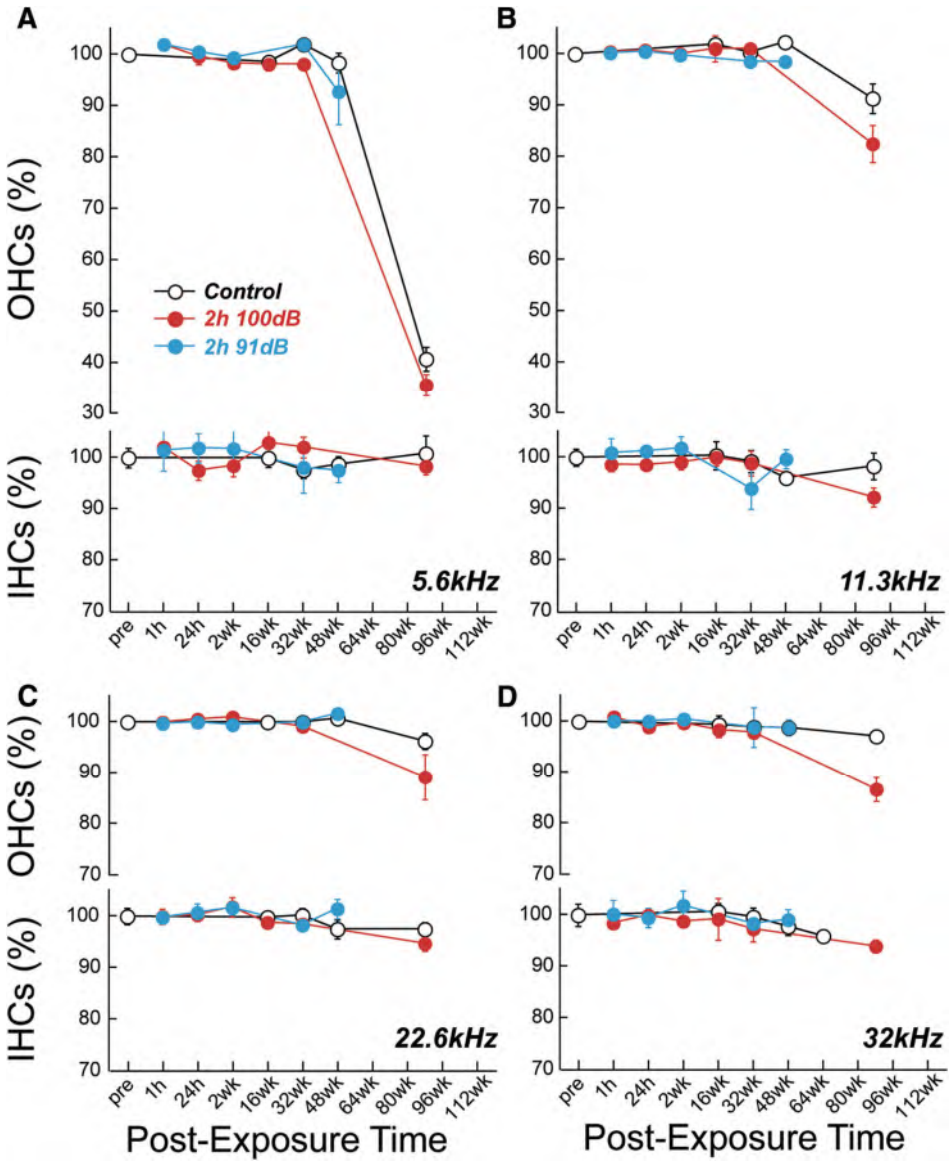

Figure 7. Synaptopathic noise exposure exacerbates OHC loss in aging ears. In unexposed ears, age-related OHC loss begins late, and, except at 5.6 kHz, is minimal (~5%) and similar in all rows. Exaggerated OHC loss was a late consequence of synaptopathic noise (100 dB, 2 h), whereas nonsynaptopathic noise (91 dB) produced no additional hair cell loss through 48 weeks after exposure. Here, we compare counts of first-row OHCs compared with 16 week unexposed controls at four cochlear frequencies for the two exposure groups and age-matched controls (***A***–***D***, upper panels of each). IHC loss was <5% at all frequencies for all groups at all ages (***A***–***D***, lower panels of each). Data are means ± SE; group sizes are provided in Figure 3 legend.

ric of noise-induced and age-related damage, are insensitive to diffuse synaptopathy; therefore, the hearing loss that results is "hidden" (Schaette and McAlpine, 2011; Bharadwaj et al., 2014; Plack et al., 2014).

In the current studies, the 91 dB, 2 h exposure differed by design from the 100 dB, 2 h exposure in that it caused no acute synaptopathy. DPOAE and ABR thresholds, as well as suprathreshold amplitudes, recovered by 2 weeks and remained identical to age-only controls for at least 1 year after exposure. Importantly, ongoing loss of synapses and ganglion cells in these ears was not different from age-only controls. Data from this nonsynaptopathic exposure thus provide several key insights. First, they provide an important control for other, stress-induced differences between exposed and unexposed animals; for example, changes in circulating glucocorticoid levels that might be induced by any 2 h, TTS-producing noise exposure regardless of the cochlear injury elicited (Canlon et al., 2007; Peppi et al., 2011). Second, the finding that ABR amplitudes recover in TTS ears lacking noise-induced synaptopathy is an important demonstration that the Wave 1 amplitude assay can provide a specific, as well as sensitive, reflection of underlying synaptic health. Third, the data provide evidence that, although synapse loss is a primary and early consequence of noise exposure, not all TTS-producing exposures are synaptopathic.

Our initial approach to the study of noise-induced cochlear synaptopathy was to create a severe TTS "on the border" of reversibility wherein even a few decibels of increase in exposure level would have caused permanent threshold shift and hair cell

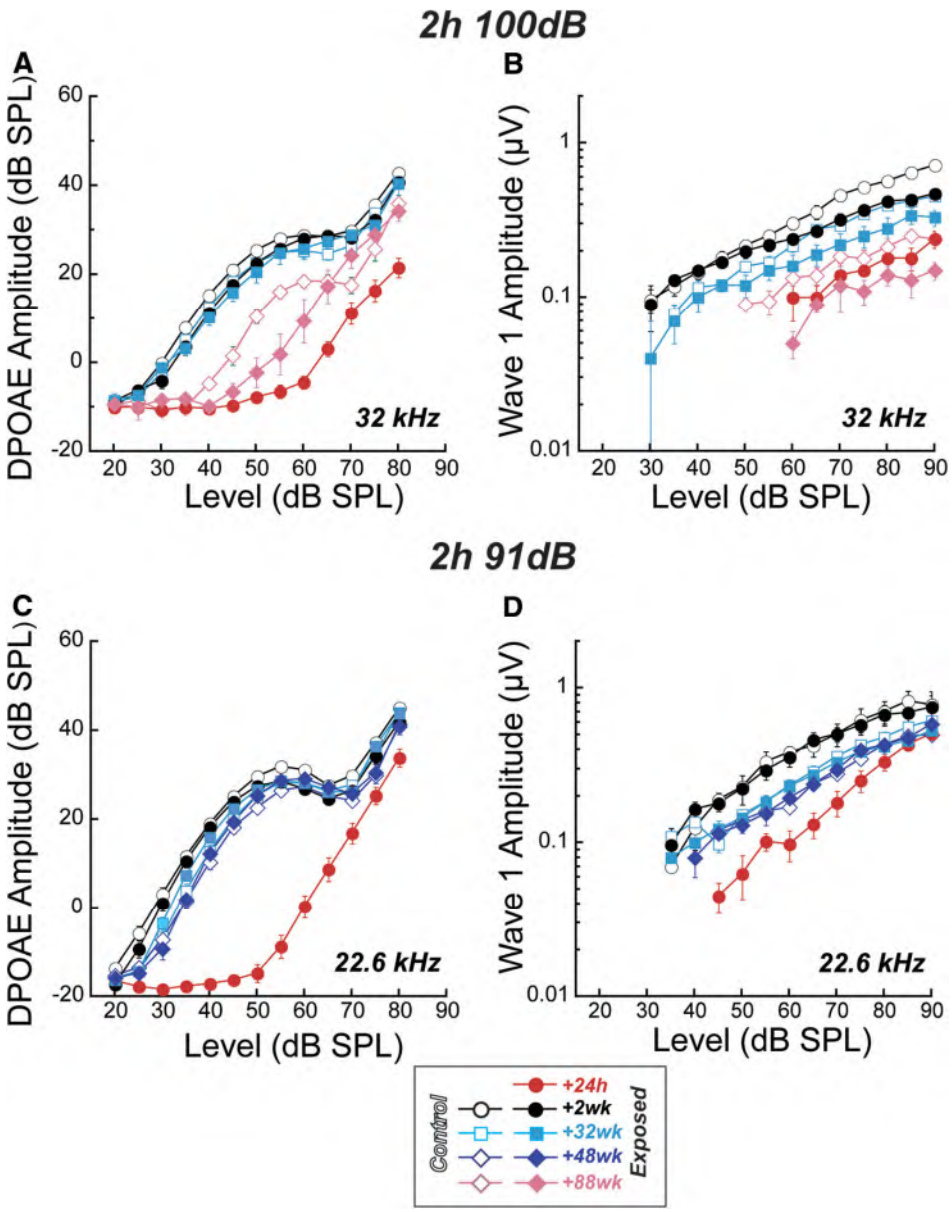

Figure 8. Synaptopathic noise exposure exacerberates ABR amplitude reductions in aging ears. DPOAE and ABR Wave 1 response growth is compared in aging ears with and without prior noise exposure. DPOAE amplitude reductions are small in unexposed ears (controls, open symbols in ***A***, ***C***) until the oldest age (***A***). In contrast, Wave 1 in unexposed ears (***B***, ***D***) shows progressive decline throughout the lifespan. Noise-exposed ears are compared at the frequency of maximum TTS for each exposure. Although thresholds recovered, synaptopathic noise (100 dB, 2 h) exaggerated the ABR (***B***), but not DPOAE (***A***), amplitude declines at all postexposure time points, with a subset plotted here, for clarity. After nonsynaptopathic noise (91 dB, 2 h), DPOAE and ABR Wave 1 responses were similar to those in control ears, at least to 48 weeks after exposure. Key in ***A*** applies to all panels. Data are means ± SE; group sizes are provided in Figure 3 legend.

damage (Kujawa and Liberman, 2009). In the adult (16 week) CBA/CaJ mouse, this was achieved with 100 dB, 2 h exposure to a noise band that produced maximum reversible threshold elevation at high frequencies and an ~40% loss of synapses in corresponding cochlear regions. Here, comparing effects of this 100 dB exposure with an exposure at a lower sound level shows that the degree of synaptopathy does not relate in a simple way to the TTS magnitude (Fig. 10). At 32 kHz, where the TTS was larger for 100 dB exposure than for 91 dB exposure (35 vs 15 dB, respectively), the synaptic loss also was much larger (40% loss vs no loss, respectively). However, at 22 kHz, where the TTSs were virtually identical, the synaptic degeneration was very different (40% loss vs no loss, respectively). The same trend can be seen by comparing the 2 h versus 8 h exposures at 91 dB: threshold shifts through ~18 kHz are the same, but the synaptopathy diverges (Fig. 5). It may be significant that, in both comparisons, the exposure producing the greater spread of TTS toward the cochlear base produced the greater loss of cochlear nerve synapses.

We wondered whether there was a trading relation between time and intensity in the generation of the synaptic loss. Commonly, "exchange rates" are used to describe relationships between exposure level and time predicted to yield equivalent noise

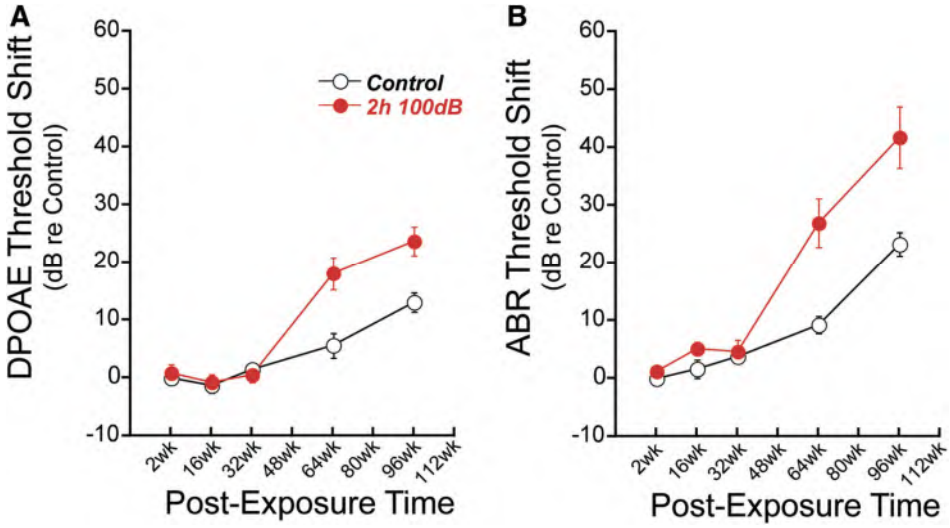

Figure 9. Synaptopathic noise exposure exaggerates threshold shifts in aging ears. After 1 synaptopathic (100 dB, 2 h) exposure at 16 weeks, thresholds return to baseline by 2 weeks after exposure (Fig. 1 *A*, *B*), but exposed mice show larger subsequent threshold shifts than controls as they age after noise. Shown here for 32 kHz, shifts for both DPOAE (***A***) and ABR (***B***) diverged at 64 weeks after exposure and were greater in the ABR. Data are means ± SE; group sizes are provided in Figure 3 legend. All shifts are calculated relative to thresholds in 16 week unexposed mice. Key in ***A*** applies to both panels.

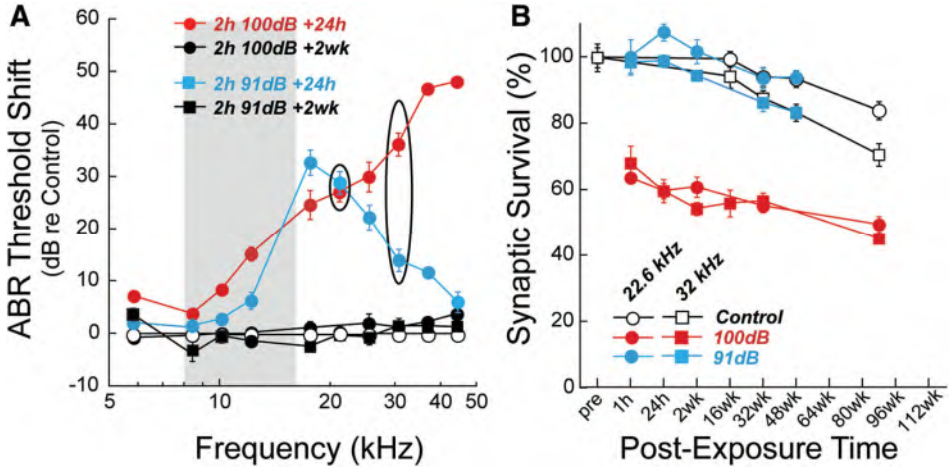

Figure 10. TTS magnitude does not predict synaptopathy. Both the 91 dB and the 100 dB exposures produced large transient threshold elevations (***A***), although shifts from the latter were larger and spread farther toward the cochlear base. Synapse loss in the 32 kHz region was seen for 100, not 91 dB exposure (***B***). At 22.6 kHz, the acute threshold shifts are identical from the two exposures (***A***); however, the higher level exposure produced large synapse loss while the lower level exposure produced none (***B***). Data are means ± SE; group sizes are provided in Figure 1 legend.

risk, and thus to establish permissible exposure levels for occupational exposure (Occupational Safety and Health Organization, 1981). The Occupational Safety and Health Organization (OSHA) uses a criterion of 90 dB for 8 h, and a 5 dB decrement/increment for every doubling/halving of exposure duration. Therefore, 95 dB exposure is allowed for 4 h, 100 dB exposure for 2 h, and so on. With a criterion level of 85 dB and an exchange rate of 3 dB, National Institute for Occupational Safety and Health (NIOSH) guidelines are more conservative (NIOSH, 1998). Our 100 dB, 2 h exposure meets the OSHA standard and our 91 dB, 2 h exposure meets the NIOSH standard. The 91 dB, 8 h exposure approximates the time-intensity trade for 100 versus 90 dB exposure (OSHA). Although none of the exposures produced permanent threshold shift, the 100 dB, 2 h and 91 dB, 8 h exposures were clearly damaging to the ear. For both OSHA and NIOSH, exposure limits (dBA) assume an 8 h work day 5 d/wk over a working lifetime; therefore, our findings cannot be compared directly. Nevertheless, they provide a framework from which to begin reconsideration of noise risk.

Vulnerability of neuronal subgroups

In our models of primary cochlear neurodegeneration, loss of IHC synapses and type I afferent neurons are proportional and subtotal, reaching no more than ~50% until hair cell loss commences. This subtotal loss may reflect a differential vulnerability among afferent fiber subtypes. Mammalian auditory nerve fibers can be grouped by spontaneous rates (SRs) of firing. Fibers with high thresholds (~40% of the population) have low SRs and fibers with low thresholds (~60%) have high SRs (Liberman, 1978; Tsuji et al., 1997). Low-SR neurons preferentially disappear

from the fiber samples in acoustically traumatized cats (Liberman and Kiang, 1978) and guinea pigs (Furman et al., 2013) and in aged gerbils (Schmiedt et al., 1996). Low- and high-SR fibers arise from peripheral terminals on opposite sides of the IHC (Liberman, 1982) and immunostaining for glutamate transporters, which take up synaptic glutamate, is less intense on the modiolar side of the IHC, where low-SR synapses predominate (Furness and Lawton, 2003). Furthermore, low-SR fiber terminals have fewer mitochondria (Liberman, 1980) and thus may be less able to buffer the Ca^{2+} overload that is important in the genesis of glutamate excitotoxicity (Szydlowska et al., 2010).

The remaining 5% of auditory nerve fibers, the type II fibers contacting OHCs, do not show the acute terminal swelling seen in type I terminals after overstimulation or perfusion of glutamate agonists (Robertson, 1983; Pujol et al., 1993). The relative invulnerability of the type II terminals likely arises because they do not express the same AMPA-type glutamate receptors (e.g., GluA2) as type I terminals (Matsubara et al., 1996; Liberman et al., 2011).

Noise–age interactions and application to humans

Declines in hearing function with age are multifactorial and there is general agreement that noise exposure is a common contributor. It is estimated that 10 million people in the United States have "hearing loss"; that is, permanent threshold elevation, related to their noise exposure (NIOSH, 2013). Permanent noise-induced threshold shifts combine with age-related shifts (Kujawa and Liberman, 2006) in ways that remain unclear, but whatever the combination, their presence can interfere with communication and compromise quality of life.

In addition to the high prevalence of permanent noise-induced threshold shifts, it is likely that exposure to TTS-producing noise affects a dramatically larger proportion of the population. Although traditionally not considered of lasting significance due to recovered thresholds, the work presented here shows that such exposures can have permanent and progressive consequences for aging ears and hearing.

Attempts to characterize such a noise–age relationships in the human have focused on audiometric thresholds and have failed to yield consensus opinions (Gates et al., 2000; Rosenhall, 2003; Lee et al., 2005; Cruickshanks et al., 2010). Here, using genetically identical animals receiving highly stereotyped exposures with all other variables held constant between exposed and unexposed age-matched cohorts, late exacerbations in threshold shifts were seen as animals aged after noise. Although OHCs are not lost acutely from the exposures studied here, exaggeration of age-related DPOAE threshold shifts and OHC losses after synaptopathic noise, particularly at high frequencies, suggest progressive involvement of cochlear amplifier function. It is possible that noise exposure also leads to early onset of sublethal changes in the expression levels of key proteins such as prestin (Xia et al., 2013).

Beyond these hair cell losses and corresponding threshold elevations, we present clear evidence that prior noise dramatically exacerbates synaptic and neural losses that otherwise occur with aging. These changes begin much earlier in time and progress as animals age after noise to involve cochlear regions that initially appeared unaffected by the exposure. The data suggest that, for such interactions to occur between noise and aging, a key requirement is the acute production of some degree of exposure-induced synaptopathy, perhaps in the cochlear base.

The fact that apparently reversible noise damage can have dramatic long-term consequences in amplifying age-related sensorineural hearing loss is of significance in the consideration of noise-risk assessment for human populations. Such findings also are intriguing in light of human temporal bone studies showing steady loss of cochlear neuronal populations with age, even in the absence of hair cell loss (Makary et al., 2011); additional study will be required to determine whether this loss is preceded by synapse loss and if it is accelerated by noise exposure, as has been demonstrated here. Humans show increasing difficulties discriminating speech in noisy environments through middle and old age, even when audibility remains normal (Snell and Frisina, 2000; Grose et al., 2006). Beyond any loss of audibility, accelerated and exaggerated loss of synaptic connections between IHCs and cochlear nerve fibers likely contributes to problems hearing in noise (Bharadwaj et al., 2014) and to central changes associated with persistent tinnitus (Knipper et al., 2013), both common in noise-exposed and aging groups.

Together, the present results demonstrate that a single synaptopathic exposure has effects on the aging ear that continue long after the noise has stopped. Further, whereas therapeutic efforts that aim to protect hair cells and thresholds from age-related and noise-induced declines are important, they appear to target events occurring rather late in the degenerative processes that we have characterized.

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Current concepts in age-related hearing loss: Epidemiology and mechanistic pathways

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Abstract

Age-related hearing loss (AHL), also known as presbycusis, is a universal feature of mammalian aging and is characterized by a decline of auditory function, such as increased hearing thresholds and poor frequency resolution. The primary pathology of AHL includes the hair cells, stria vascularis, and afferent spiral ganglion neurons as well as the central auditory pathways. A growing body of evidence in animal studies has suggested that cumulative effect of oxidative stress could induce damage to macromolecules such as mitochondrial DNA (mtDNA) and that the resulting accumulation of mtDNA mutations/deletions and decline of mitochondrial function play an important role in inducing apoptosis of the cochlear cells, thereby the development of AHL. Epidemiological studies have demonstrated four categories of risk factors of AHL in humans: cochlear aging, environment such as noise exposure, genetic predisposition, and health co-morbidities such as cigarette smoking and atherosclerosis. Genetic investigation has identified several putative associating genes, including those related to antioxidant defense and atherosclerosis. Exposure to noise is known to induce excess generation of reactive oxygen species (ROS) in the cochlea, and cumulative oxidative stress can be enhanced by relatively hypoxic situations resulting from the impaired homeostasis of cochlear blood supply due to atherosclerosis, which could be accelerated by genetic and co-morbidity factors. Antioxidant defense system may also be influenced by genetic backgrounds. These may explain the large variations of the onset and extent of AHL among elderly subjects.

1. Introduction

Age-related hearing loss (AHL), or presbycusis, is a complex degenerative disease and is one of the most prevalent chronic conditions of the aged, affecting tens of millions of people world-wide. AHL is a multifactorial condition, representing the end stage sequela of multiple intrinsic (e.g. genetic predisposition) and extrinsic (e.g. noise exposure) factors

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acting on the inner ear over a lifetime that cumulatively lead to impairments in cochlear transduction of acoustic signals (Ohlemiller, 2009; Schuknecht, 1955).

Potential sites of pathology include the inner and outer hair cells, the stria vascularis, and afferent spiral ganglion neurons (Schuknecht et al., 1993). The stria vascularis and hair cells are particularly susceptible to injury. The stria vascularis is highly metabolically active and depends on an elaborate cellular machinery to maintain the steady-state endocochlear resting potential. Consequently, injury from multiple different pathways (e.g. age-related cell losses within the stria, oxidative stress from noise exposure, genetic polymorphisms leading to inefficient oxidative pathways or dysfunctional supporting cells, or microvascular disease in the strial vessels) could all affect strial function (Ohlemiller, 2009). The resulting loss of the endocochlear potential would impair the function of the cochlear amplifier and lead to an increase in hearing thresholds (Schmiedt et al., 2002; Schuknecht et al., 1974).

A similar multimodal pathway of injury and dysfunction is also observed in the cochlear hair cells and cochlear nerve. Post-mitotic hair cells are susceptible to accumulated injury over time from a combination of poor cellular repair mechanisms associated with aging, direct mechanical or mitochondrial oxidative injury from noise, and toxicity from aminoglycosides or other ototoxic medications (Liu et al., 2007; Ohlemiller, 2004; Pickles, 2008). Neuronal degeneration of spiral ganglion afferents can also be triggered by cumulative exposures to loud noise leading to glutamate excito-toxicity and loss of the afferent dendrites (Kujawa et al., 2006). Interestingly, such a mechanism of injury may allow for relative preservation of pure tone threshold sensitivity but disproportionate effects on speech perception in noise and speech understanding given the complexity of speech sounds and the need for precise temporal and frequency coding by the spiral ganglion afferents.

The complexity of factors (aging, genetic, epigenetic, environmental, health co-morbidity) and importantly the interaction of the different mechanistic pathways that can cause AHL have greatly complicate our interpretation of basic and clinical research into AHL (Van et al., 2007) and have led to some latent cynicism about the precise value of key factors contributing to AHL (Ohlemiller, 2009). In particular, the same functional consequences of *increased hearing thresholds* and *poor frequency resolution* generally occur regardless of etiology of AHL or the cochlear mechanistic pathway (Pickles, 2008). Consequently, for elderly with AHL, the main issue is often the inability to understand words rather than the inability to hear, leading to the refrains of “I can hear you but I can’t understand you” or perhaps more commonly, “My hearing is fine. You’re just mumbling”. Most importantly, AHL gradually impairs an individual’s ability to understand the meaning of everyday language (e.g. “I’ll see you *Sunday*” versus “I’ll see you *someday*”), in which fine auditory cues encoding semantic meaning are critical for understanding communicative meaning.

In this review, we have chosen to focus on recent works that have improved our understanding of the cellular and molecular mechanisms that could cause age-related degeneration of the cochlea. Particularly, we have emphasized the role of oxidative stress and mitochondrial dysfunction due to accumulation of mitochondrial DNA (mtDNA) mutations/deletions in the development of AHL.

2. Human studies

2.1. Prevalence of ARHL

Estimating hearing loss prevalence and identifying epidemiologic risk factors can be ascertained from large cohorts where audiometric testing was performed. A sampling of such studies include Beaver Dam (Cruickshanks et al., 2003), Framingham (Gates et al.,

1990), Blue Mountains (Gopinath et al., 2009), Baltimore Longitudinal Study of Aging (BLSA) (Brant et al., 1990), and National Health and Nutrition Examination Survey (NHANES) (Agrawal et al., 2008). Reports of hearing loss prevalence across these studies vary because of different tonal frequencies utilized to obtain a pure tone average (PTA), monaural or binaural definition of hearing loss, and audiometric cutoffs used to define hearing loss. Differences in cohort characteristics (volunteer cohort or recruitment of population sample) and the age of the cohort also limit comparisons across studies.

A useful audiometric definition of hearing loss has been adopted by the World Health Organization as a speech-frequency pure tone average of thresholds at 0.5, 1, 2 and 4 kHz tones in the better-hearing ear of >25 dB (World Health Organization). The selected tonal frequency range and the use of the better-hearing ear are useful from a pragmatic perspective that emphasizes communication since 0.5–4 kHz represents the critical frequency range of speech, and the better-hearing ear would be the principal determinant of a person's communicative abilities. Using this definition of hearing loss and NHANES data (representing a cross-section of the non-institutionalized U.S. population), hearing loss prevalence approximately doubles every decade of life from the second through seventh decades (Fig. 1) (Lin et al., 2011a). Using the same definition of hearing loss, national Institute for longevity sciences-longitudinal study of aging (NILS-LSA) in Japan has reported that the prevalence rates of AHL are 29% in late sixties, 39% in early seventies, and 65% in late seventies in male, and 23%, 37%, and 59% in female, respectively (http://www.ncgg.go.jp/department/ep/monograph5th/sensory.htm).

Other reports of hearing loss prevalence have generally focused on older adults using differing definitions of hearing loss. Prevalence rates have been 29% (>26 dB in the standard PTA [0.5–2 kHz] in the better ear, subjects >60 years), 73% (>25 dB in the speech frequency [0.5–4 kHz] PTA in the worse ear, subjects >70 years), and 60% (>25 dB in the standard PTA in the worse ear, subjects 73–84 years) in the Framingham (Gates et al., 1990), Beaver Dam (Cruickshanks et al., 1998b), and Health ABC (Helzner et al., 2005) studies, respectively. Using identical definitions of hearing loss and age ranges from the latter two studies, prevalence figures calculated using the 2005–2006 NHANES dataset would be 76% and 64%, respectively (Lin et al., 2011a). However, comparing results across different studies is difficult even when applying the same definition of hearing loss given the different demographic characteristics across cohorts particularly with regard to age and race. For example, both the Framingham cohort and Beaver Dam cohorts included few African American individuals, but the Health ABC cohort included 36.3% African American. Age distributions and ranges also varied across these study cohorts. Strength of using NHANES estimates of hearing loss prevalence is that these results are generalizable to the entire civilian, non-institutionalized U.S. population.

2.2. Risk factors for AHL

Epidemiologic studies also provide insight into the modifiable and non-modifiable risk factors associated with hearing loss and provide further insight into the mechanistic pathways underlying AHL. Studied risk factors can generally be divided into four categories as discussed previously (Cooper, 1994; Cruickshanks et al., 1998a, 2003): cochlear aging (individual age), environment (occupational and leisure noise exposure, ototoxic medications, socioeconomic status), genetic predisposition (sex, race, specific genetic loci/genes), and health co-morbidities (hypertension, diabetes, stroke, cigarette smoking). Strong and consistent associations of hearing loss have generally been found with the non-modifiable risk factors of increasing age (increased risk), male sex (increased risk), and African American (decreased risk) (Agrawal et al., 2008; Brant et al., 1990; Gates et al., 1990; Helzner et al., 2005; Ishii et al., 1998; Jerger et al., 1986).

Genetic predisposition as shown by heritability studies among twins and longitudinal studies of family cohorts have also shown heritability indices of 0.35–0.55 (Christensen et al., 2001; Gates et al., 1999; Karlsson et al., 1997), indicating that genetic phenotype accounts for a substantial portion of hearing loss risk. Using general estimation equation analysis, Shimokata (2008) found that 28 out of 177 single nucleotide polymorphisms (SNPs) were associated with impaired hearing in the elderly subjects. Of these, 5 SNPs were significantly related to hearing impairment at low frequencies (125–500 Hz) and other 5 SNPs at high frequencies (2–8 kHz), respectively. The SNPs associated hearing loss at low frequencies were distinct from those at high frequencies, but all these SNPs are known to be associated with atherosclerosis or obesity. The odds ratio of hearing impairment between subjects with all 5 SNPs and those with none of them was 18.6 (95% confidence interval, 4.9–70.8) at low frequencies and 6.5 (95% confidence interval, 3.3–12.7) at high frequencies.

Other factors that have associations with the risk of hearing loss include hypertension and cardiovascular disease, cerebrovascular disease, smoking, diabetes, noise exposure, and alcohol consumption, with all factors being associated with increased risk of hearing loss except for alcohol consumption (Cruickshanks et al., 1998a, 1998b; Dalton et al., 1998; Gates et al., 1993; Helzner et al., 2005; Van et al., 2007; Shimokata, 2008).Cruickshanks et al. (1998a) evaluated the association between smoking and hearing loss in 3753 adults aged 48–92 years, and found that after adjusting for other factors, current smokers were 1.69 times as likely to have a hearing loss as nonsmokers (95% confidence interval, 1.31–2.17), with weak evidence of a dose–response effect. Similarly,Fransen et al. (2008) conducted a multicenter study to elucidate the environmental and medical risk factors contributing to AHL and found that in 4083 subjects between 53 and 67 years, smoking significantly increased high-frequency hearing loss with dose-dependent effect. There have been some inconsistent findings with the latter group of risk factors, which may be a consequence of how hearing loss was defined and the characteristics of the study cohort. For example, noise exposure may primarily lead to high-frequency hearing loss, whereas cardiovascular risk-factors affect both low and high-frequencies. Averaging across frequencies when defining a pure tone average could, therefore, obscure certain associations depending on which tonal frequencies are selected for the PTA. Characteristics of the study cohort may also obscure potential associations depending on the risk factors present in the risk group. For example, in a study focused on only older adults, the factors associated with older age and cochlear aging may overshadow associations with these weaker risk factors. Genetic heterogeneity within cohorts with consequent variability in gene-risk factor interactions (Liu et al., 2007; Van et al., 2007) would also likely bias any possible association toward the null hypothesis.

Previous research into hearing loss epidemiology has emphasized the study of modifiable risk factors in order to form the basis for possible hearing loss prevention strategies. However, the contribution of these modifiable risk factors (e.g. hypertension, etc.) is relatively weak in comparison to the non-modifiable risk factors of genetic predisposition and race as demonstrated by the consistency and strength of associations seen in epidemiologic studies. Further study of these non-modifiable risk factors, particularly the physiologic basis of black race being a protective factor for hearing loss and the identification of the genetic loci and genes contributing to AHL, could possibly offer the most substantial and profound insights into actual hearing loss prevention.

2.3. Impact of race on AHL

Previous observational studies investigating the role of race and hearing loss have consistently demonstrated that black race is associated with a 60–70% lower odd of noise-induced hearing loss and AHL compared to white subjects (Agrawal et al., 2008; Cooper, 1994; Helzner et al., 2005; Lin et al., 2011b). Other epidemiologic studies using a case–control approach recruiting individuals with similar occupational exposures have also

demonstrated a reduced risk of hearing loss in black subjects (Ishii et al., 1998; Jerger et al., 1986). A recent epidemiologic study suggests that skin color and hence melanocytic functioning in the cochlea is the mechanism underlying the protective association of race with hearing (Lin et al., 2011b).

Melanin produced by strial melanocytes (intermediate cells) in the cochlea has been hypothesized to serve a protective role as a free radical scavenger, metal chelator, or regulator of calcium homeostasis in the stria vascularis, which is involved with generating and maintaining the endolymphatic potential necessary for normal hearing (Murillo-Cuesta et al., 2010; Riley, 1997). A recent study has also demonstrated that deficiency in strial melanin is associated with marginal cell loss and decline in the endocochlear potential (Ohlemiller et al., 2009). There have not been any further epidemiologic studies exploring the issue of race and hearing loss and little basic science research into mechanistic pathways leading to hearing preservation in individuals with darker skin. The lack of research exploring these topics is surprising, given the strength of the epidemiologic association between race and hearing loss and the fact that melanin pathways in the inner ear could potentially be pharmacologically targeted for hearing loss prevention.

2.4. Candidate genes associated with AHL

The number of genetic investigations on AHL has increased at a surprising rate recently. Association studies analyze genetic variations in unrelated individuals and try to identify those variations that are more frequent in affected individuals compared to unaffected individuals. The ultimate in association studies is a genome-wide association study (GWAS), in which hundreds of thousands of SNPs across the entire genome are analyzed in unrelated individuals. Although the use of GWAS to understand human disease is maturing, GWAS remain prohibitively expensive, and sometimes association studies are limited to a carefully selected set of candidate genes. To date, only several GWAS studies have been performed (Huyghe et al., 2008; Konings et al., 2009; Van et al., 2007, 2008, 2010; Friedman et al., 2009; Girotto et al., 2011); however, these studies have been limited in only studying a certain subset of potential genes or markers (i.e. those associated with monogenic forms of deafness) rather than examining a broad array ($>10^6$) of various polymorphisms.

Candidate-gene-based association studies also have been extensively carried out recently. This approach is based on the selection of candidate genes, which are usually implicated in a biological pathway that is plausibly related to a specific disease. A whole range of candidate genes can be proposed because perception of sound involves many complex pathways and age-related changes in any component of one such pathway could contribute to AHL. Genes causing monogenic forms of hearing loss are candidate susceptibility genes for AHL and other genes can be candidates because of a known or presumed function in the inner ear. With these considerations in mind, a number of researchers have speculated that oxidative stress, and consequently, mitochondrial DNA mutations, have important causative roles in the development of AHL. Several genes and loci have been proposed using candidate gene approaches (see review by Uchida et al., 2011), which included DFNA18 and DFNA5 loci, chromosome 8q24, 13-kb region of KCNQ4 (Potassium channel, voltage gated, subfamilyQ, member 4), N-acetyltransferase 2 grainyhead like 2, glutamate receptor metabotropic 7, glutathione S-transferase (GST), apolipoprotein E allele 34, endothelin-1 (EDN1), mitochondrial uncoupling protein 2 (UCP2), and mitochondrial DNA mutations.

Interestingly, some of the candidate genes are well known to be associated with oxidative stress and atherosclerosis. For example, GSTs, one of glutathione-related antioxidant enzymes, catalyze conjugation of glutathione with xenobiotics and other compounds and play an important role in the antioxidant protection of the cochlea (el Barbary et al., 1993). Decreased glutathione and GST activity levels cause increased susceptibility of cells to

insults and cell damage. When glutathione level is lower, cochlea becomes more vulnerable to intense noise (Yamasoba et al., 1998) and aminoglycoside-induced hearing loss (Lautermann et al., 1995). Van Eyken et al. (2007) investigated an association between AHL and genes related to oxidative stress using a large set of 2111 independent samples from two population groups, the general European and the Finnish population. Although they did not detect an association between *GSTM1* (mu, chromosome 1p13.3), or *GSTT1* (theta, chromosome 22q11.2) and AHL in the former population, there were significant associations between both genes and AHL in the latter population.

UCPs are members of the larger family of mitochondrial anion carrier proteins They facilitate the transfer of anions from the inner to the outer mitochondrial membrane and the return transfer of protons from the outer to the inner mitochondrial membrane and also reduce the mitochondrial membrane potential in mammalian cells. UCPs play a role in non-shivering thermogenesis, obesity, diabetes and atherosclerosis, but the main function of UCP2 is the control of mitochondria-derived ROS (Arsenijevic et al., 2000). Recently,Sugiura et al. (2010) reported that UCP2 Ala55Val polymorphisms, but not UCP1 A-3826G polymorphism, exhibited significant association with AHL in the Japanese population.

Endothelin is a potent vasoactive peptide that is synthesized and released by the vascular endothelium and the best-characterized endothelin, EDN1, is involved in the development of atherosclerosis. Several SNPs in *EDN1* gene have been shown to be associated with atherosclerosis, coronary disease and hypertension (for example, Yasuda et al., 2007). Further, EDN1 can induce a strong, long-lasting constriction of the spiral modiolar artery, causing an ischemic stroke of the inner ear (Scherer et al., 2005).Uchida et al. (2009) has observed significant association between the Lys198Asn (G/T) polymorphism (rs5370) in the *EDN1* gene and hearing loss in middle-aged and elderly Japanese.

2.5. Mitochondrial DNA mutations and AHL

Increases of deletions, mutations, or both in mtDNA have been reported in human archival temporal bone samples from people with AHL compared to normal hearing control tissues.Bai et al. (1997) examined mtDNA from celloidin-embedded temporal bone sections of 34 human temporal bones, 17 with normal hearing and 17 with AHL, and found that a 4977-base pair (bp) deletion, called a ‘common ageing deletion,’ was significantly more frequent in the cochlear tissues from patients with AHL compared to those with normal hearing.Markaryan et al. (2009) evaluated the association between the common ageing deletion level in cochlear tissue and the severity of hearing loss in elderly subjects and found that a mean level of the deletionwas 32 ± 14% in subjects with AHL and 12 ± 2% in the normal-hearing age-matched controls, with statistical significance. They also observed the reduction of cytochrome *c* oxidase subunit 3 (COX3) expression in spiral ganglion cells from individuals with AHL, and in addition to the mtDNA common ageing deletion, other deletions involving the mtDNA major arc contributed to the observed deficit in COX 3 expression (Markaryan et al., 2010). Sporadic mtDNA mutations are also likely to contribute to the manifestation of AHL. Fischel-Ghodsian et al. (1997) examined the archival temporal bones from five patients with AHL for mutations within the mitochondrially-encoded cytochrome oxidase II gene and when compared to controls, the mutations occurred more commonly with AHL despite great individual variability in both quantity and location of mutation accumulation.

3. AHL studies in animals

3.1. General pathological and physiological findings

As discussed earlier, AHL is generally classified into three major types based on the relationship between cochlear pathology and hearing levels: sensory (loss of sensory hair cells), neuronal (loss of spiral ganglion neurons), and metabolic (strial atrophy) hearing loss (Schuknecht, 1955). Age-related stria atrophy or degeneration is one of the common features of AHL in both animals and humans (Gates and Mills, 2005; Ohlemiller, 2009; Fetoni et al., 2011). Aged gerbils display loss of stria capillaries (Gratton and Schulte, 1995), degeneration of marginal and intermediate cells of the stria vascularis (Gates and Mills, 2005; Spicer and Schulte, 2005), and loss of Na^+K^+ ATPase (Schulte and Schmiedt, 1992), which regulates stria function and endocochlear potential (EP) through transporting Na^+ out, while transporting K^+ into the cell (Spicer and Schulte, 2005). The loss of function of the cells in the stria vascularis and/or spiral ligament is thought to result in disruption of inner ear ion homeostasis, thereby causing a decline in EP. Consistent with this view, aged gerbils display an age-related decline in EP as well as disruption of ion homeostasis in the cochlea (Schmiedt, 1996).

There are several mouse models of aging and age-related diseases that display a variety of premature aging phenotypes, including a reduced lifespan and early onset of AHL. C57BL/6J mouse strain, one of the most widely used models for the study of aging and age-associated diseases, display loss of the hair cells and spiral ganglion neurons and increased hearing thresholds by 12 months of age (Zheng et al., 1999). Aged C57BL/6 mice display an age-related decline in the density of spiral ligament and stria vascularis (Ichimiya et al., 2000) and also an age-related decrease in the cross-sectional area of the stria vascularis as well as the survival of the Type IV fibrocytes in the spiral ligament (Hequembourg and Liberman, 2001). Interestingly, an age-related decline in EP was observed in CBA/CaJ mice and BALB/cJ mice, but not in C57BL/6 or CBA/J (Lang et al., 2002; Sha et al., 2008), which suggests that decreased EP may not be a key common feature of AHL. Since inbred mouse strains have a wide range of noise sensitivities and rates of hearing loss with age, they may not be good model for the heterogeneity of the human population. An animal population featuring a genetically heterogenous background, late onset of hearing loss and a well defined range of sensitivity to environmental factors might provide a more informative model for human AHL.Schacht et al. (2012) tested four-way cross mice from 4 parental strains, MOLF/Ei, C3H/HeJ, FVB/NJ, and 129/SvImJ, and identified several polymorphisms affecting hearing in later life (loci on chromosomes 2, 3, 7, 10, and 15 at 18 months, on chromosomes 4, 10, 12, and 14 at 22 months in noise-exposed mice, and on chromosomes 10 and 11 in those not exposed to noise). Such four-way cross mice, in which each in the progeny shares a random 50% of its genetic heritage with each other, are considered to have the advantages of providing robustness, reproducibility, and genetic tractability (Miller et al., 1999) and thus are worth for future AHL studies.

3.2. Role of ROS in AHL

It has been postulated that reactive oxygen species (ROS) play a major role in the degeneration of these cochlear cells during aging (Cheng et al., 2005; Someya et al., 2009). It is now well established that mitochondria are a major source of ROS (Balaban et al., 2005; Lin and Beal, 2006; Wallace, 2005) and that the majority of intra-cellular ROS are continuously generated as a by-product of mitochondrial respiration metabolism during the generation of ATP (Balaban et al., 2005; Beckman and Ames, 1998; Halliwell and Gutteridge, 2007). These ROS include superoxide ($\bullet O_2^-$) and hydroxyl radical (•OH) which are extremely unstable, and hydrogen peroxide (H_2O_2) which is freely diffusible and relatively long-lived (Balaban et al., 2005; Beckman and Ames, 1998; Halliwell and

Gutteridge, 2007). ROS generated inside mitochondria are hypothesized to damage key cell components such as nuclear DNA, mitochondrial DNA (mtDNA), membranes, and proteins. Such oxidative damage accumulates over time and leads to tissue dysfunction during aging. This by no means is in any way special to the inner ear, but has been ubiquitously found in all systems. An elaborate antioxidant system has evolved to control the damaging effects of those ROS. The system includes the antioxidant enzymatic scavengers, such as superoxide dismutase (SOD), catalase, GST, and glutathione peroxidase (Gpx) (see Halliwell and Gutteridge, 2007). SOD decomposes superoxide (O_2^-) into hydrogen peroxide (H_2O_2) and oxygen (O_2), while catalase and Gpx decomposes hydrogen peroxide into water (H_2O) and oxygen (Halliwell and Gutteridge, 2007).

It has been shown that increased Gpx activity was observed in the stria vascularis and spiral ligament in the cochlea of aged Fisher 344 rats (Coling et al., 2009). In the organ of Corti of CBA mice, glutathione-conjugated proteins, markers of H_2O_2-mediated oxidation, began to increase at 12 months of age and 4-hydroxynonenal and 3-nitrotyrosine, products of hydroxyl radical and peroxynitrite action, respectively, were elevated by 18 months, whereas antioxidant proteins AIF and enzymes SOD2 decreased by 18 months (Jiang et al., 2007). Age-related cochlear hair cell loss was enhanced in mice lacking the antioxidant enzyme *SOD1* (McFadden et al., 1999), and reduced thickness of the stria vascularis and severe degeneration of spiral ganglion neurons were observed in middle-aged *SOD1* knockout mice (Keithley et al., 2005). Similarly, mice lacking senescence marker protein 30 (SMP30)/gluconolactonase (GNL), which could not synthesize vitamin C (VC), showed reduction of VC in the inner ear, increased hearing thresholds, and loss of spiral ganglion cells, suggesting that VC depletion accelerates AHL (Kashio et al., 2009). Conversely overexpression of catalase in the mitochondria reduced oxidative DNA damage in the cochlea and slowed AHL in C57BL/6 mice (Someya et al., 2009). These findings implicate that oxidative damage in the cochlea reflects an age-related decline in the antioxidant defenses and/or an age-related increase in ROS levels and pays a crucial role in the development of AHL.

Several studies have been conducted to examine the effects of antioxidants against AHL. Seidman (2000) conducted a randomized prospective study over a 3-year period, in which Fischer 344 rats were given vitamin E, VC melatonin, or lazaroid, and observed that the antioxidant-treated animals had better auditory sensitivities and a trend for fewer mtDNA deletions compared with placebo subjects.Seidman et al. (2002) also examined the effects of lecithin, a polyunsaturated phosphatidylcholine that plays a rate-limiting role in the activation of numerous membrane-located enzymes including SOD and glutathione, on aging and AHL. When Harlan–Fischer rats aged 18–20 months were divided into controls and experimental group supplemented orally for 6 months with lecithin, lecithin-treated animals showed significantly better hearing sensitivities, higher mitochondrial membrane potentials, and less common ageing mtDNA deletion in the cochlear tissues including stria vascularis and auditory nerve compared to controls. Le and Keithley (2007) demonstrated that aged dogs fed a high antioxidant diet for the last 3 years of their life showed less degeneration of the spiral ganglion cells and stria vascularis compared to dog fed control-diet.

In C57BL/6 mice, supplementation with VC did not increase VC levels in the cochlear tissue or slow AHL (Kashio et al., 2009), but animals fed with diet comprising six antioxidant agents (L-cysteine-glutathione mixed disulfide, ribose-cysteine, NW-nitro-L-arginine methyl ester, vitamin B12, folate, and ascorbic acid) exhibited significantly better hearing sensitivity than controls (Heman-Ackah et al., 2010). When C57BL/6 mice were fed with control diet or diet containing one of 17 antioxidant compounds (acetyl-L-carnitine, α-lipoic acid, carotene, carnosine, coenzyme Q10, curcumin, tocopherol, EGCG, gallic acid,

lutein, lycopene, melatonin, poanthocyanidin, quercetin, resveratrol, and tannic acid), AHL was nearly completely prevented by α-lipoic acid and coenzyme Q_{10} and partially by *N*-acetyl-L-cysteine, but not by other compounds (Someya et al., 2009). In CBA/J mice, antioxidant-enriched diet containing vitamins A, C, and E, L-carnitine, and α-lipoic acid given from 10 months through 24 months of age significantly increased the antioxidant capacity of the inner ear tissues but did not ameliorate AHL or loss of the hair cells and spiral ganglion cells (Sha et al., 2012). These findings indicate that supplementation with certain antioxidants can slow AHL in animals but that the effects depends on many factors, including the type and dosage of anti-oxidant compounds, timing and duration of the treatment, species, and strains. Defining these factors and those we've yet to identify is one of the goals in future research.

3.3. Effect of calorie restriction against AHL

Caloric restriction (CR) extends the lifespan of most mammalian species and is the only intervention shown to slow the rate of aging in mammals. Maximum lifespan is thought to be increased by reducing the rate of aging, while the average lifespan can be increased by improving environmental conditions. In laboratory rodents, CR delays the onset of age-related diseases such as lymphomas, prostate cancer, nephropathy, cataracts, diabetes, hypertension, and hyperlipidemia, and autoimmune diseases (see Sohal and Weindruch, 1996; Mair and Dillin, 2008). Despite such evidence, the question remains whether CR also acts to retard aging and disease in higher species such as non-human primates and humans. In monkeys, CR has been reported to result in signs of improved health including reduced body fat, higher insulin sensitivity, increase in high-density lipoprotein and reduction in very low-density lipoprotein levels (Rezzi et al., 2009). Twenty-year longitudinal adult-onset CR study in rhesus macaques maintained at the Wisconsin National Primate Research Center (WNPRC) demonstrated that moderate CR lowered the incidence of aging-related deaths and delayed the onset of age-associated pathologies, such as diabetes, cancer, cardiovascular disease, and brain atrophy (Colman et al., 2009). Very recently, a CR regimen implemented in young and older age rhesus monkeys at the National Institute on Aging (NIA) has been shown not to improve survival outcomes, contrast with an ongoing study at WNPRC, suggesting a separation between health effects, morbidity and mortality (Mattison et al., 2012).

It is difficult to determine whether CR has beneficial effects on longevity and age-related diseases in humans because there are no validated biomarkers that can serve as surrogate markers of aging and because it is impractical to conduct randomized, diet-controlled, long-term survival studies in humans. Nonetheless, data from epidemiologic studies suggest that CR may have beneficial effects on the factors involved in the pathogenesis of primary and secondary aging and life expectancy in humans. Food shortages during World War in European countries were associated with a sharp decrease in coronary heart disease mortality, which increased again after the war ended (Hindhede, 1921; Strom and Jensen, 1951). Another study among Spanish nursing home residents undergoing long-term alternate day feeding regimen also demonstrated decreased morbidity and mortality (Vallejo, 1957). In addition, inhabitants of Okinawa island, who ate ≈30% fewer calories than the rest of Japanese residents, had ≈35% lower rates of cardiovascular disease and cancer mortality than the average Japanese population and had one of the highest numbers of centenarians in the world (Kagawa, 1978). Due to the Westernization on the nutrition, resulting in increased meat intake and fat energy ratio and decreased intake of beans and vegetables, the longest life expectancy at birth for men in Okinawa is now no higher than the national average in Japan, reflecting increased mortality ratio due to heart disease and cerebrovascular disease (Miyagi et al., 2003). It should be noted, however, that these associations do not prove

causality between decreased calorie intake and increased survival and that CR studies in humans did not always show influence on age-related changes.

The preventive effect of CR against AHL has been inconsistent across reports (see review by Someya et al., 2010a). Fischer rats that were calorie restricted to 70% of the control intake beginning at one month of age and then housed for 24–25 months showed significantly better hearing thresholds, reduced hair cell loss, and decreased mtDNA common deletion in the auditory nerve and stria vascularis of the cochlea compared to controls (Seidman, 2000). CR also delayed the onset of AHL in the AU, CBA and B6 strains of mice, but not in the DBA, WB, or BALB strains. Beneficial effects by CR have been reported in monkeys maintained at WNPRC, but not in those at NIA. Interestingly, high fat diet given for 12 month, which is opposite to CR, elevated hearing thresholds at high-frequency region and increased ROS generation, expressions of NADPH oxidase and UCP, accumulation of mtDNA common deletion, and cleaved caspase-3 and TUNEL-positive cells in the inner ear of Sprague–Dawley rats (Du et al., 2012).

The underlying mechanisms for the CR-associated benefits remain unclear.Someya et al. (2007b) observed that C57B/6 mice that received CR by 15 months of age retained normal hearing and showed no obvious cochlear degeneration and a significant reduction in the number of TUNEL-positive cells and cleaved caspase-3-positive cells in the spiral ganglion cells compared to age-matched controls; microarray analysis also revealed that CR down-regulated the expression of 24 apoptotic genes, including *Bak* (BCL2-antagonist/killer 1) and *Bim* (BCL2-like 11), suggesting that CR could prevent apoptosis of the cochlear cells. In addition, oxidative stress by paraquat induced *Bak* expression and apoptosis in primary cochlear cells, which was ameliorated in Bak-deficient cells (Someya et al., 2009). Furthermore, a mitochondrially targeted catalase transgene and oral supplementation with α-lipoic acid and coenzyme Q_{10} suppressed *Bak* expression in the cochlea, reduced cochlear cell death, and prevented AHL, suggesting that oxidative stress induces Bak-dependent apoptosis in the cochlear cells (Someya et al., 2009). It has recently been reported that CR failed to reduce oxidative DNA damage and prevent AHL in C57B/6 mice lacking the mitochondrial deacetylase Sirt3, a member of the sirtuin family (Someya et al., 2010b). In response to CR, Sirt3 directly deacetylated and activated mitochondrial isocitrate dehydrogenase 2 (Idh2), leading to increased NADPH levels and an increased ratio of reduced-to-oxidized glutathione in mitochondria. In cultured cells, overexpression of Sirt3 and/or Idh2 increased NADPH levels and protected from oxidative stress-induced cell death. These findings strongly suggest that at least a primary mechanism underlying the beneficial effects of CR is mediated by ROS-antioxidant systems and that Sirt3 is essential in enhancing the mitochondrial glutathione antioxidant defense system in the cochlea during CR.

3.4. Mitochondrial dysfunction and mitochondrial DNA mutations in AHL

Recent development of DNA microarray analysis has provided a global analysis of gene expression in the aging tissues. Someya et al. (2007a) compared gene expression profiles in the cochlea between 2-month-old and 8-month-old DBA/2J and found that AHL was associated with profound down-regulation of genes involved in the mitochondrial respiratory chain complexes in the cochlea of aged DBA/2J mice. A comparison of cochleae from middle aged C57B/6 mice under CR and normal control diet revealed that genes involved in apoptosis were down-regulated whereas those involved in mitochondrial function and DNA repair were up-regulated as a result of CR (Someya et al., 2007b).

As discussed before, mtDNA mutations and common ageing deletions have been reported to increase with aging in human temporal bones (Bai et al., 1997; Markaryan et al., 2009, 2010; Fischel-Ghodsian et al., 1997). It has been shown that accumulation of mtDNA

mutations leads to premature aging in mitochondrial mutator mice (*Polg* knockin mice), indicating a causal role of mtDNA mutations in mammalian aging (Kujoth et al., 2005; Trifunovic et al., 2004). The *Polg* knockin mice were created by introducing a two base substitution, which results in a defect in mtDNA proof-reading ability. Young *Polg* mutator mice were indistinguishable from wild-type WT littermates, but 9–10 months old mutator mice displayed a variety of premature aging phenotypes, including early onset of AHL, severe loss of the spiral ganglion neurons, degeneration of the stria vascularis, and increase of TUNEL-positive spiral ganglion cells, while age-matched wild-type mice displayed only minor loss/degeneration of the cochlear cells (Someya et al., 2008). DNA microarray analysis revealed that mtDNA mutations were associated with transcriptional alterations consistent with impairment of energy metabolism, induction of apoptosis, cytoskeletal dysfunction, and hearing dysfunction in the cochlea of aged *Polg* mutator mice.Niu et al. (2007) also reported that the mtDNA mutator mice showed progressive apoptotic cell loss in the spiral ganglion, increased pathology in the stria vascularis, and accelerated progressive degeneration in the neurons in the cochlear nucleus compared to wild-type mice. These findings imply that accumulation of mtDNA mutations lead to mitochondrial dysfunction, an associated impairment of energy metabolism, and the induction of an apoptotic program in the cochlea.

4. Putative mechanisms of AHL

As discussed above by reviewing recent human and animal studies, it is now well established that oxidative stress and mtDNA mutations/deletions play a crucial role in the development of AHL. Substantial evidence has accumulated from animal studies that cumulative effect of oxidative stress could induce damage to macromolecules such as mtDNA in the cochlea and that the resulting accumulation of mtDNA mutations/deletions and decline of mitochondrial function over time progressively induce (Bak-dependent) apoptosis of the cochlear cells. Epidemiological human studies have demonstrated four categories of risk factors of AHL, i.e., cochlear aging, environment such as noise exposure, genetic predisposition, and health co-morbidities such as cigarette smoking and atherosclerosis. Genetic investigation has identified several putative associating genes, including those related to antioxidant defense system and atherosclerosis. Exposure to noise is known to induce excess generation of reactive oxygen species (ROS) in the cochlea, and cumulative oxidative stress can be enhanced by relatively hypoxic situations resulting from the impaired homeostasis of cochlear blood supply due to atherosclerosis, which could be accelerated by genetic and co-morbidity factors. Antioxidant defense system may also be influenced by genetic backgrounds including race. The conceptual figure of the model for the development of AHL has been shown in Fig. 2. This may explain the large variations of the onset and extent of AHL among elderly subjects. AHL has been shown to be slowed by certain interventions, such as CR and supplementation with antioxidants, in laboratory animals. Large clinical trials are needed to investigate if AHL can be delayed or prevented in humans and gain insights into the molecular mechanisms of AHL. Given the social value, quality of life and economic costs of AHL and the safety of many of the potentially effective interventions, we hope that such trials will begin in the near future.

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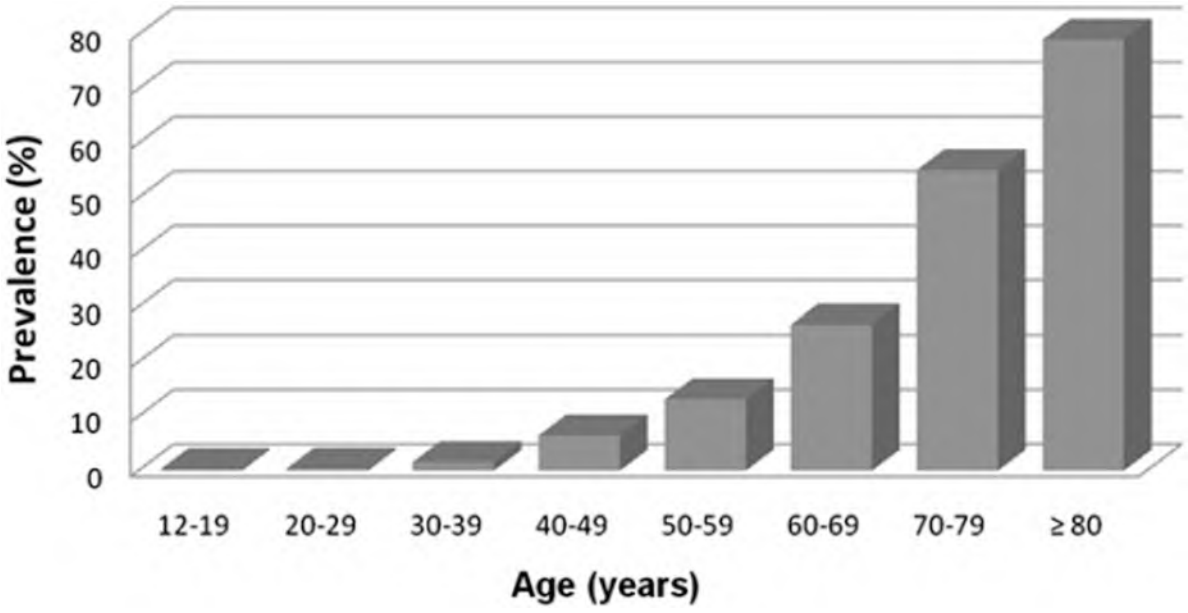

Fig. 1.
Prevalence of hearing loss in the United States by age, 2001–2008. Hearing loss is defined by a PTA of 0.5–4 kHz thresholds in the better-hearing ear >25 dB.

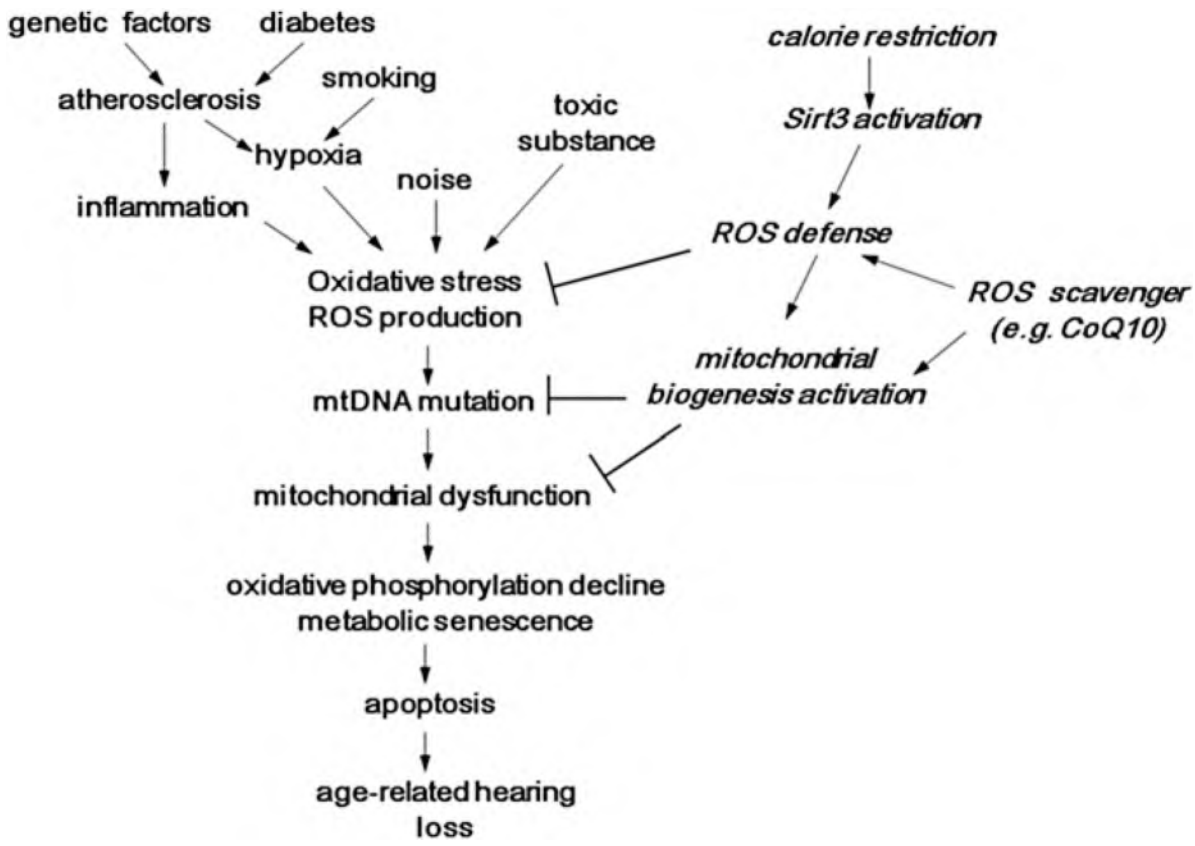

Fig. 2.
Conceptual model of the development of age-related hearing loss.

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COMMENT OPEN

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What is the safe noise exposure level to prevent noise-induced hearing loss?

Daniel Fink [1]✉

Keywords: Health Studies; Personal Exposure; Population Based Studies

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INTRODUCTION

Exposure to noise causes noise-induced hearing loss (NIHL) [1] and two other auditory disorders, tinnitus and hyperacusis [2]. This Comment will focus on answering the question, "What is the safe noise exposure level to prevent NIHL?" The exposure-response relationship between noise and hearing loss in humans has been studied in the occupational setting for decades [3]. Based on thousands of laboratory studies in a variety of animal models, the mechanisms by which noise exposure causes NIHL are also well understood, down to the ultrastructural, biochemical, and genetic effects of noise on cochlear hair cells and synaptic junctions [4, 5]. The exposure-response relationships for tinnitus and hyperacusis have not been established, though, and the mechanisms of injury are not yet understood. Ninety per cent of people with tinnitus also have hearing loss [6]. Knowledge of the safe noise exposure level to prevent NIHL should also help people avoid developing noise-induced tinnitus, and probably hyperacusis as well.

NOISE CAUSES HEARING LOSS

It has been known since the eighteenth century, if not earlier, that men working in certain occupations- blacksmiths, stonemasons, and bell ringers among them- couldn't hear well. After the development of gunpowder, hearing loss became common in soldiers and sailors [7]. The first report of occupational noise-induced hearing loss (NIHL) is said to be that of Ramazzini in 1713 among coppersmiths in Venice [8]. During the industrial age, hearing loss in workers making steam boilers was so common that it became known as boilermaker's disease [7]. The U.S. National Institute for Occupational Safety and Health (NIOSH) was established in 1970, and published recommended exposure limits for occupational noise in 1972 [9]. These recommendations were updated in 1998. NIOSH is part of the U.S. Centers for Disease Control and Prevention (CDC) but it wasn't until 2015 that CDC recognized that noise exposure caused NIHL in the public, not just in workers with occupational exposure [10].

The anatomy of the auditory system is illustrated in Fig. 1 [11]. The physiology of hearing and the details of mechanotransduction are well described [12]. Sound waves collected and focused by the external ear (pinna) cause vibrations in the ear drum (tympanic membrane) which are communicated via three tiny bones in the middle ear to the cochlea, where they cause distortion of cochlear hair cells, the basic sensory organ of hearing. The hair cell distortions in turn cause chemical changes transduced into electrical impulses, which are transmitted via cochlear synapses to the auditory nerve, and thence to the auditory processing cortex in the brain where they are perceived as sound.

The mechanisms by which loud noise damages cochlear structures are well-understood, down to the ultrastructural, molecular, and genetic levels [4, 5]. The damage noise exposure does to cochlear hair cells, the basic sensory receptors for hearing, is shown at the bottom in Fig. 1. Animal research over the last two decades has also demonstrated that noise damages cochlear synapses [13], with recent confirmation of the same effects in post-mortem studies of human temporal bone specimens [14]. This damage is thought to be the major cause of speech-in-noise difficulty, the difficulty following one conversation among many in a noisy environment. Speech-in-noise difficulty is called hidden hearing loss because patients complaining of difficulties understanding speech often have normal or near normal audiograms. The prevalence of speech-in-noise difficulty is reported to be 10–15% of the adult population, but since speech-in-noise testing is not done during screening audiometry, it may be higher [15].

The Equal Energy Hypothesis states that equal amounts of sound energy will produce equal amounts of hearing impairment, regardless of how the sound energy is distributed in time [9]. A useful albeit imperfect analogy for the effect of noise exposure on the ear is the effect of sun exposure on the skin. Both NIHL and deep wrinkles and pigment changes are the results of exposures to energy, the first of cochlear hair cells to sound energy and the second of the skin to solar energy. Drooping of the skin (ptosis) is part of normal aging, due to the downward force of gravity on collagen fibers, but without sun exposure, the skin remains smooth and unwrinkled into old age [16]. Without excessive noise exposure, auditory sensitivity (hearing) remains normal into old age [17]. The analogy is imperfect because ultraviolet components of sunlight cause direct DNA damage in the skin, whereas noise

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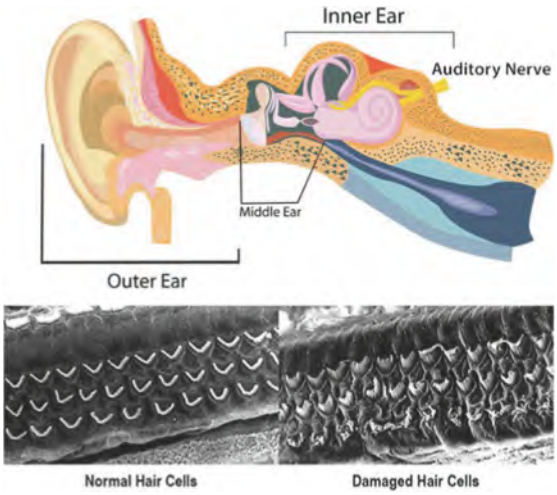

Fig. 1 Top: Auditory structures from external ear (pinna) to auditory nerve. Bottom: Normal and damaged hair cells. From Centers for Disease Control and Prevention. How does loud noise cause hearing loss? [11].

exposure can damage inner ear structures directly and also leads to chemical changes damaging or killing cochlear hair cells.

Average noise exposure measurements obscure the impact of brief high-intensity noise exposures, called impulse or impulsive noise, which have a disproportionate impact on auditory health [18, 19]. Intermittent noise exposure is difficult to study in the occupational setting, and is subsumed into calculated recommended averages for occupational noise exposure [9], but this may underestimate the impact of non-Gaussian noise exposure [18]. The effect of impulse noise on the public has not been systematically studied, with only anecdotal news and case reports of impulse noise exposure causing hearing loss, tinnitus, or hyperacusis. For both occupational and non-occupational noise exposure, greater attention must be paid to impulse noise. A dermatologic analogy for the disproportionate impact of impulsive noise on hearing may be the fact that one severe sunburn in childhood or adolescence has been correlated with the development of melanoma in adult years [20].

NOISE INDUCED HEARING LOSS IS A MAJOR CAUSE OF DISABILITY

NIHL is a major problem in the United States and the world. Approximately 25% of American adults age 20–69 have noise-induced hearing loss, half with no significant occupational noise exposure [21]. According to the CDC, hearing loss is the third most common chronic physical condition in the United States [22]. Globally, an estimated 5% of the world's population has NIHL [1]. The 2019 Global Burden of Disease Study found that hearing loss is the fourth leading cause of disability globally [23]. In the United States and Europe, approximately 30–50% of adults over age 65 have hearing loss great enough to affect communication [24, 25]. The prevalence of hearing loss increases to approximately 80% over age 80, with almost everyone reaching the tenth decade of life having hearing loss [26].

There are many causes of hearing loss- infections, ototoxic drugs, genetic diseases among them- but the most common cause of hearing loss with age is NIHL, the result of a lifetime of cumulative excess noise exposure [17, 27]. Hearing loss is not a benign condition. In addition to communication difficulties, which in younger individuals can affect success in school and in the workplace leading to reduced lifetime earnings [28], hearing loss in older people is correlated with many adverse health effects. These include increased risk of falls, social isolation, depression, dementia, accidents, and hospitalization and death [29]. The only current approved treatments for hearing loss are amplification (with hearing aids) and cochlear implantation, the latter reserved for the profoundly hearing impaired [29]. There is a stigma associated with hearing loss [30] and a high non-usage rate for those who have acquired hearing aids [31]. Unfortunately, hearing aids do not restore normal hearing and do not provide an auditory correction similar to the visual correction provided by lenses [32]. Hearing aids are also costly, and no country can afford to provide them to all its citizens who need them. But even in countries where hearing aids are provided by national health programs, there are still many people who do not wear hearing aids [33]. Hearing aid non-use may be common because while hearing aids help people hear better in quiet ambient noise situations, amplification is less helpful in high ambient noise situations [34]. Newer digital hearing aids with tunability and frequency band adjustment features are advertised as being more helpful than older analog models, but as yet no published peer-reviewed research has confirmed this. Perhaps more importantly, it is obvious from looking at the photomicrographs in Fig. 1 that delivering amplified sound waves to dead or damaged cochlear hair cells is unlikely to help hearing as much as desired.

HEARING LOSS IS NOT PART OF NORMAL AGING

What is often called *age-related hearing loss* or *presbycusis* largely represents the effects of cumulative lifetime noise exposure on the ears [27]. Figure 2 shows that actual *age-related hearing loss* in a population not exposed to loud noise is approximately only a 10 dB decrement at age 70 [17]. This hearing threshold level does not meet standard criteria for hearing loss [35].

It has been postulated that factors other than noise exposure are important causes of hearing loss with age, e.g., genetic factors, exposure to ototoxic substances, diabetes, smoking, hypertension, or atherosclerosis. These factors and others are indeed correlated with hearing loss. However, studies done in the 1960s in isolated populations not exposed to loud noise found preservation of auditory sensitivity into old age. The best known of these may be that by Rosen et al. in the Mabaan population of the Sudan [36].

The importance of noise exposure as a cause of hearing loss was subsequently demonstrated in the 1986 study by Goycoolea et al. [37]. Using a natural experiment study design, they found that hearing loss was more prevalent in Easter Island residents who had left the remote, very quiet island to seek employment on the noisier South American mainland than in those who had remained at home. They concluded that noise exposure the most important factor, stating that,

> *"With all factors being equal, except exposure to modern civilization, our results showed that living in civilized societies has a significant negative effect on hearing; the severity is directly proportional to the years of exposure."*

The fact that noise was the most important contributor to hearing loss in old age was confirmed by the 2020 study of donated temporal bone specimens by Wu et al. [14]. They stated,

> *"…the larger, and more functionally significant, basal loss in humans is largely noise-induced. If true, the bad news is that we are all abusing our ears, to our significant functional detriment, as we age."*

Most people living in industrialized societies are exposed to everyday noise levels sufficient to cause NIHL [38, 39]. but are almost entirely unaware that they are "abusing their ears."

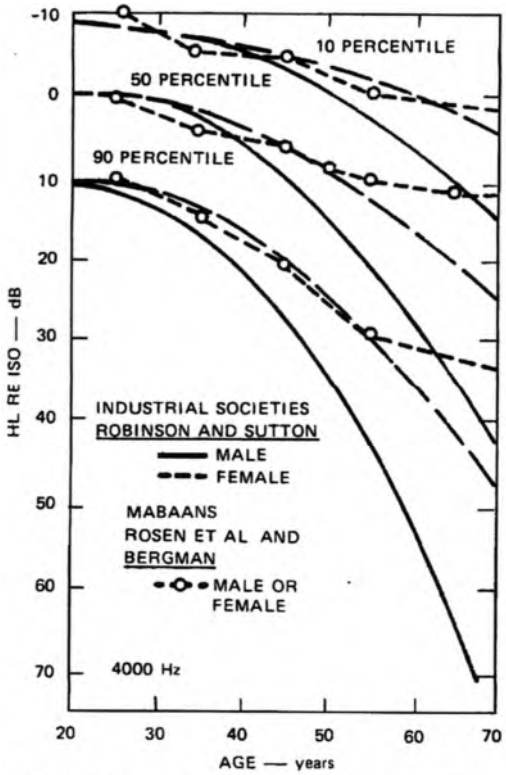

FIG. 11. HLs for young people from the studies of Mabaans and industrialized societies, and the differences in HLs for the older age groups. Test frequency, 4000 Hz. The raw data points for the Mabaans are plotted 10 dB higher (re: 15–25-year-olds) than reported on assumption of audiometer calibration error (see text).

Fig. 2 Hearing levels for Mabaans and industrialized societies. Figure is reproduced with permission of the Acoustical Society of America from ref. [17].

PREVENTING NOISE-INDUCED HEARING LOSS

Prevention of disease is better and less expensive than treatment or rehabilitation [40]. The U.S. Centers for Disease Control and Prevention state that "hearing loss from noise is 100% preventable" [41]. Again, what is the actual safe noise exposure level to prevent noise-induced hearing loss (NIHL)? This cannot be the NIOSH recommended exposure limit (REL) of 85 A-weighted decibel (dbA) for occupational noise, first calculated in 1972 and revised in 1998 [9]. Occupational noise exposure limits do not prevent NIHL, even if they are often wrongly cited as safe for the public or as the sound pressure level at which auditory damage begins [42]. The NIOSH REL allows an 8% excess risk of occupational NIHL; the 90 dBA U.S. Occupational Safety and Health Administration permissible exposure limit allows a 25% excess risk [9]. Even if members of the public are not exposed to noise 8 h/day, 50 weeks/year, for 40 years, these are not safe noise exposure levels, not for workers, certainly not for the public, and especially not for children.

The only evidence-based safe noise exposure level to prevent NIHL, the U.S. Environmental Protection Agency's (EPA) calculated 70 dB time-weighted daily average ($Leq_{(24)} = 70$) for the public [43, 44], can no longer be considered safe, either. One reason the EPA's 70 dB level may not prevent NIHL is that, as discussed above, disproportionate auditory damage can be caused by brief high-intensity noise exposures obscured by average noise exposure measurements, recommendations, or calculations. More importantly, everyday noise exposure now begins in early childhood and continues at home and from recreational activities during working years and then after retirement.

Consequently, both occupational noise exposure limits and the EPA's safe noise level must be revised downwards to reflect increased non-occupational noise exposure. For both occupational exposure limits and public noise exposure calculations, three additional factors must be considered [45]: 1) cumulative lifetime noise exposure, now approaching 80 years, not just 40-year adult noise exposure histories; 2) detection of noise-induced auditory damage by more sensitive methods than limited-frequency pure tone audiometry, such as extended range audiometry, speech-in-noise testing, and questions about tinnitus and hyperacusis [46]; and 3) use of a zero hearing threshold level rather than 15 dB hearing threshold level used by NIOSH as the standard for normal hearing [47].

WHAT IS THE ACTUAL SAFE NOISE EXPOSURE LEVEL TO PREVENT NIHL?

Why does knowing the actual safe noise exposure level matter? Without knowing the safe noise exposure level, it is impossible to accurately advise both workers and the public on how to protect their hearing. For the public, if a condition is an inevitable part of normal physiological aging, e.g., thinning, graying hair, nothing can be done to prevent it. If the condition is not inevitable, e.g., muscle weakness, obesity, hypertension, and diabetes, behavioral changes can prevent or at least delay the onset of the condition [27]. For NIHL, avoidance of loud noise exposure or use of hearing protection devices can prevent the development of what is commonly called age-related hearing loss.

How can we answer the question, "What is the actual safe noise exposure level to prevent NIHL?" Due to modern ethical and legal protections for human research subjects, one cannot design a study purposefully exposing them to sufficient noise to damage their hearing to assess how much noise exposure causes hearing loss. A > 80-year observational study correlating measured or estimated lifetime noise exposure with hearing loss would be costly and difficult to complete. Fortunately, historical studies may provide an answer. Before modern research subject protections were established, noise-induced temporary threshold shift (NITTS), the temporary decrease in auditory sensitivity after loud noise exposure, was used as a measure of auditory damage from noise [48]. NITTS is seen immediately after noise exposure, but largely resolves over time (See Fig. 3.).

With repeated exposures, NITTS eventually becomes noise-induced permanent threshold shift, i.e., NIHL. This persistent damage is suggested by the residual decrease in auditory sensitivity at 24 h after exposure in the green line in Fig. 3. Figure 3 also shows the audiometric notch, the concentration of hearing loss around 4 kHz, which is considered pathognomonic for NIHL [49].

NITTS is a real and measurable phenomenon. Additionally, any auditory symptoms after noise exposure, including tinnitus, likely indicate that permanent auditory damage has occurred [50]. The sound pressure level needed for the human ear to recover from NITTS, the effective quiet level, is approximately 55 dBA [51]. This is probably the safe noise exposure level to prevent NIHL from a single exposure, with 55–60 dB time-weighted average being the actual safe noise exposure level for a day.

This analysis is not new. Almost 30 years ago, Kryter wrote,

> *"Several investigators, using human and animal subjects, have found that recovery from Temporary Threshold Shift is reduced when the level of background noise in periods between exposures to more intense noise was no higher than L_A 50–70 dB. Not until the "noise" in the recovery periods was less than those levels did full recovery continue. This maximum level, perhaps for humans*

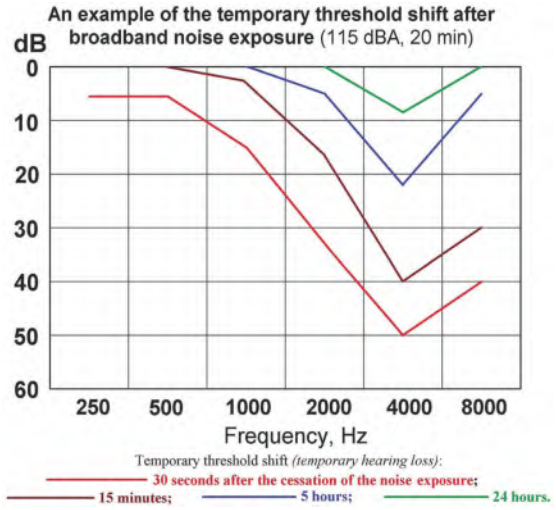

Fig. 3 Noise-induced temporary threshold shift. From ref. [56]. Published under Creative Commons CO 1.0 Universal Public Doman Dedication.

around L_A55 for an octave band and L_A60 for broadband noise, is called effective quiet, and presumably indicates a level, perhaps a 24-h, $EL_{Aeq,24h}$, energy level, required for complete avoidance by the average, and 50%ile, ear of sound induced permanent threshold shifts during a lifetime [51].

The 55 dBA effective quiet level likely represents the sound pressure level at which reversible intracellular chemical processes involved in hearing are overwhelmed, eventually causing noise-induced hearing loss. This hypothesis must be confirmed by animal studies. Fifty-five dBA is approximately the sound pressure level of human speech in a quiet environment [52]. It appears that humans evolved to be able to communicate with each other without damaging our hearing, but any sounds greater than the relatively low sound pressure level of speech may cause auditory damage.

CONCLUSION

Based on Kryter's analysis, the safe noise exposure level to prevent NIHL is about 55–60 dB time-weighted average for a day. Since any temporary auditory discomfort, tinnitus, or NITTS likely indicates that permanent auditory damage has occurred, it is possible that the safe noise exposure level for impulse noise is also only 55 dBA. These sound pressure levels are radically lower than current occupational noise exposure recommendations, the EPA's calculated safe noise level, or any published guidance for public noise exposure. There is no reason to question Kryter's 30-year old analysis of human data, but these proposed safe noise levels need to be confirmed by laboratory studies using appropriate animal models.

Terminology matters. The commonly used terms *presbycusis* and *age-related hearing loss* misleadingly imply that hearing loss is an inevitable part of normal aging. More accurate terms may be Kryter's *sociocusis* [17] or *noise-induced hearing loss in the elderly* (*NIHL-E*). The standard definition of noise, *noise is unwanted sound*, does not accurately reflect the harm that noise does. Wanted sound, e.g., at a rock concert or from power tool use, can cause NIHL, and unwanted sound is stressful and has adverse non-auditory health effects. A better definition is *noise is unwanted and/or harmful sound* [53]. This new definition of noise opens the abstract of the 2021 American Public Health Association policy statement *Noise as a Public Health Hazard* [54] and was adopted for use in 2023 by the International Commission on Biological Effects of Noise and added to its Constitution [55].

Three things- the new definition of noise, an understanding that hearing loss with age is not part of normal physiological aging but largely represents noise damage, and public awareness of a lower safe noise exposure level to prevent NIHL- may prompt at least some individuals to reduce noise exposure for themselves and their children. Lower occupational noise exposure limits may lead to recommendations or regulations for lower public noise exposure. Even if wrongly cited as safe for the public, lower occupational noise limits would also reduce public noise exposure. CDC states that NIHL is the only type of hearing loss that is entirely preventable. Prevention of disease is better and less expensive than treatment. Knowledge that both wanted and unwanted noise are harmful, combined with awareness of the actual safe noise exposure level to prevent NIHL, may help both workers and members of the public prevent NIHL.

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Hidden Hearing Loss: A Disorder with Multiple Etiologies and Mechanisms

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Hidden hearing loss (HHL), a recently described auditory disorder, has been proposed to affect auditory neural processing and hearing acuity in subjects with normal audiometric thresholds, particularly in noisy environments. In contrast to central auditory processing disorders, HHL is caused by defects in the cochlea, the peripheral auditory organ. Noise exposure, aging, ototoxic drugs, and peripheral neuropathies are some of the known risk factors for HHL. Our knowledge of the causes and mechanisms of HHL are based primarily on animal models. However, recent clinical studies have also shed light on the etiology and prevalence of this cochlear disorder and how it may affect auditory perception in humans. Here, we review the current knowledge regarding the causes and cellular mechanisms of HHL, summarize information on available noninvasive tests for differential diagnosis, and discuss potential therapeutic approaches for treatment of HHL.

Sensorineural hearing loss affects more than 320 million people worldwide (Olusanya et al. 2014) and has traditionally been diagnosed clinically by the presence of permanently elevated auditory thresholds. This type of hearing loss is caused by the dysfunction or degeneration of inner hair cells (IHCs), outer hair cells (OHCs), and/or spiral ganglion neurons (SGNs) in the cochlea. Together, these cells are responsible for detection, encoding, and transmission of acoustic information to the central auditory circuits. Many human subjects, however, show normal auditory sensitivity (auditory thresholds), yet have significant perceptual difficulties, including understanding speech in noisy backgrounds (Halpin et al. 1994; Gordon-Salant 2005; Grose and Mamo 2010; Ruggles et al. 2011; Bharadwaj et al. 2015). Such perceptual dysfunction has often been termed "auditory processing disorder," and defects in central auditory pathways have been thought to play a key role (Chermak and Musiek 1997). However, recent studies provide evidence that changes in the peripheral auditory system (the cochlea) induced by noise, drugs, peripheral neuropathy, or aging can also alter the neural sound-evoked output of the auditory

[4]These authors contributed equally to this work.

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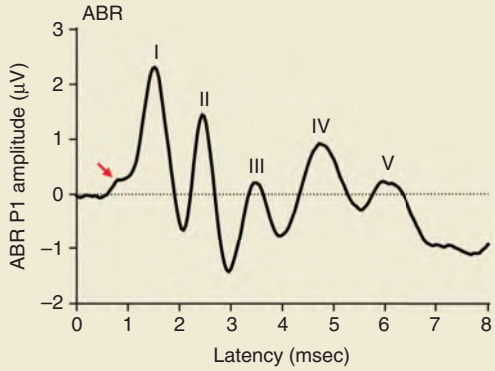
nerve (AN) independently of hair cell loss and changes in hearing thresholds. This form of hearing loss has been referred to as "hidden hearing loss" (HHL) to reflect that the dysfunction is not revealed by standard tests of auditory thresholds (audiometric test; see Box 1) (Schaette and McAlpine 2011). Based on recent surveys, the prevalence of this type of dysfunction as described by subjects with self-reported hearing difficulties despite having normal hearing thresholds has been estimated at 12%–15% (Tremblay et al. 2015; Spankovich et al. 2018).

The auditory defects associated with HHL have been shown in animal models by detection of changes in neural responses to sounds with intensities above hearing thresholds (suprathreshold sounds) in the absence of changes in sensitivity (threshold shifts). Early studies in mice indicated that moderate noise exposures that induce temporary threshold shifts (TTS) do not induce hair cell death, but rather result in decreased responses to suprathreshold sounds that persist after thresholds recover. The observation that the decreased amplitude in the response

BOX 1. AUDIOMETRIC TESTS

Audiometric threshold testing in human subjects: a psychophysical test that evaluates the sensitivity of hearing perception, typically in response to pure tones with discrete frequencies (250 to 8000 Hz) that span most of the human audible range. Sensitivity is expressed as a detection threshold on a logarithmic scale and is measured in decibels (dB) relative to a reference sound pressure level (SPL).



Auditory brainstem response (ABR): a far-field response detected by head-mounted electrodes that measures the synchronous electrical activity of the auditory system evoked by transient sounds. A typical ABR waveform obtained from a mouse in response to a pure tone is shown above, and consists of five major peaks, with peak I corresponding to activity generated by the auditory nerve within 2 msec following the sound stimulus, and the later peaks II through V corresponding to activity generated by neurons in successive nuclei of the auditory hindbrain. The small minor peak that occurs just before peak I (red arrow) is the summating potential (SP), which is generated mainly by activity of inner hair cells in the cochlea. The magnitude of peak I amplitudes correlates with the number and synchronous firing rate of the SGN fibers. Thresholds are determined by the lowest intensity of sound that will produce a recognizable waveform.

Compound action potential (CAP): a near-field response detected by electrodes at the cochlear round window in animals or at the tympanic membrane (eardrum; known as "electrocochleography") in humans. Like in the ABR, this response measures the synchronous activity of the auditory nerve that is evoked by transient sounds and the same peaks can be detected.

Distortion product otoacoustic emission (DPOAE): a sound produced by the cochlea in response to presentation of two simultaneous sounds, measured using a sensitive microphone placed in the ear canal. Production of this emitted sound depends on the amplification activity of outer hair cells in the cochlea.

to suprathreshold sounds correlates with the loss of a subset of synaptic connections between IHCs and AN fibers in the cochlea led to the notion that noise-induced synaptopathy causes HHL (Kujawa and Liberman 2009). The strong evidence for this HHL mechanism resulted in the terms synaptopathy and HHL often being used interchangeably. However, more recent findings indicate that other causes of HHL exist, including cochlear demyelination (Wan and Corfas 2017; Choi et al. 2018) and possibly mild or persistent hair cell dysfunction (Hoben et al. 2017; Mulders et al. 2018). Here, we summarize the current knowledge of HHL and discuss the diverse mechanisms that lead to the development of this pathology in animal models and humans. In addition, we review the different diagnostic tools and potential treatments for HHL.

CAUSES OF HIDDEN HEARING LOSS

Noise Exposure

Numerous studies in mice (Kujawa and Liberman 2009; Shi et al. 2015), rats (Lobarinas et al. 2017), and guinea pigs (Lin et al. 2011; Liu et al. 2012; Shi et al. 2013, 2016; Song et al. 2016) showed that moderate noise exposure induces HHL. These studies found that moderate noise exposures (e.g., 100 dB sound pressure level [SPL] for 2 hours in mice) produce acute but temporary shifts in auditory thresholds (ABR, CAP, and DPOAE, see Box 1) that recover within days or weeks (for review, see Hickox et al. 2017). These TTSs occur without hair cell loss. However, even after threshold recovery, cochlear responses to suprathreshold sound levels are significantly altered; that is, the amplitude of the first peak of the ABR waveform (ABR peak I) is reduced, consistent with a decreased number of AN fibers activated by the sound, and/or a decrease in their firing rate or synchrony. Although most early studies evaluated the effects of continuous noise, recent reports indicate that a single blast exposure may also result in HHL both in animals (Niwa et al. 2016; Hickman et al. 2018) and in humans (Bressler et al. 2017). The reduced neural responses associated with noise-induced HHL are expected to alter the coding of temporal and intensity features of suprathreshold sounds and to reduce the ability to perceive sounds in complex listening environments, such as those with background noise. The latter has been tested in rats with HHL following exposure to 109-dB SPL octave band noise, which resulted in TTS and permanent reductions in ABR peak I amplitudes (Lobarinas et al. 2017). Although thresholds recovered within 2 weeks, behavioral testing of exposed rats showed a poorer performance in a test of hearing in background noise.

In humans, the neural coding problems associated with HHL are expected to produce deficits in speech discrimination and intelligibility, especially in noisy environments (Kujawa and Liberman 2015; Wan and Corfas 2015). A number of studies are consistent with this prediction, suggesting that individuals who have experienced exposures to loud noise have greater difficulties in complex listening tasks despite near normal audiological thresholds. For example, subjects with higher reported noise exposures than controls with similar thresholds showed significant deficits in word recognition (Alvord 1983) and in accurate speech and sound detection in noisy background environments (Kujala et al. 2004; Kumar et al. 2012; Liberman et al. 2016). Furthermore, young adults with a history of exposure to loud recreational noise have problems in discrimination of bursts of narrowband sounds presented at low levels relative to those with less exposure (Stone et al. 2008). Effects of noise exposure have been reported for ABR and electrocochleogram peak I amplitudes in response to suprathreshold stimuli (Stamper and Johnson 2015; Liberman et al. 2016; Valderrama et al. 2018). Finally, a variety of physiological and perceptual measures were used by Bharadwaj et al. (2015) to investigate a group of young adult subjects (21–39 years old) with normal hearing sensitivity to determine potential relationships between coding of suprathreshold responses and perception of complex auditory stimuli. Although this study identified only "marginally significant" correlations between reported noise history and several measures of temporal coding, better temporal coding metrics were strongly associated with better perception of "competing" speech and to sounds that differ

in their binaural timing characteristics. Together, these studies highlight the importance of accurate neural coding of suprathreshold sounds, independent of auditory sensitivity, for performance in complex listening environments, and suggest that accumulated noise exposures can degrade these abilities.

However, several recent studies have failed to find significant correlations among prior noise exposure, electrophysiological measures associated with HHL and perceptual hearing ability (Kluk et al. 2016; Fulbright et al. 2017; Grinn et al. 2017; Prendergast et al. 2017a,b; Guest et al. 2018). Additionally, studies in which small negative correlations were shown between reported noise exposure and ABR peak I amplitudes, often failed to identify a clear relationship with expected perceptual dysfunction (Grose et al. 2017; Valderrama et al. 2018). Many factors may underlie the discordant studies relating noise and HHL, including inaccuracies in self-reporting of lifetime noise exposure, potential confounding effects of age and central auditory system compensation mechanisms, and the effects of different underlying mechanisms on physiological and behavioral measures of hearing.

Aging

The ability to understand speech in noisy environments decreases with age even in subjects with normal auditory thresholds in response to sounds up to at least 8 kHz (Dubno et al. 1984; Frisina and Frisina 1997; Pichora-Fuller and Souza 2003; Rajan and Cainer 2008). Likewise, aging subjects show declines in neural coding of the temporal features of sound that are likely important for speech perception in noise, and such deficits can also occur independently from increases in thresholds (Clinard and Tremblay 2013; Marmel et al. 2013; King et al. 2014). Decreases in the amplitudes of ABR peak I in aging human subjects are consistent with a cochlear neuropathy and could underlie these temporal processing defects (Konrad-Martin et al. 2012). Similar declines (>50%) across the life span in ABR peak I amplitudes have also been shown in mice (Sergeyenko et al. 2013; Muniak et al. 2018). Although these mice show a gradual increase in auditory thresholds over the course of their life span, this appears to be driven largely by OHC loss at later ages. The decreases in ABR peak I amplitudes in response to suprathreshold stimuli also progress over time but follow an earlier trajectory that parallels the pattern of IHC synapse loss (Sergeyenko et al. 2013), consistent with synaptopathy being a key contributor to age-related HHL in mice. Furthermore, Liberman and colleagues reported that a single noise exposure that causes TTS and HHL in young adult mice (4 months of age) significantly accelerates the rate of age-related overt hearing loss, including ABR threshold elevations and OHC loss. This data indicates that a single exposure to moderate noise levels (TTS type) early in life predisposes to an accelerated, progressive hearing loss across the life span (Kujawa and Liberman 2009; Fernandez et al. 2015).

Peripheral Neuropathy

A number of peripheral neuropathies can directly affect AN function and SGN survival (Rance and Starr 2015). The hearing loss associated with these disorders is often termed "auditory neuropathy," as defined by intact OHC function together with altered ABRs. Although peripheral neuropathies often result in relatively large effects on AN function and thereby alter ABR thresholds, some patients show normal hearing sensitivity yet have significant perceptual difficulties, for example, in Guillain–Barré syndrome (GBS) and Charcot–Marie–Tooth (CMT) disease. GBS is caused by transient damage to peripheral myelinating Schwann cells (Kuwabara and Yuki 2013). Intriguingly, in GBS patients who suffered acute hearing loss, although hearing threshold gradually recovered, the latency of their ABR waveforms was persistently increased, indicative of HHL (Takazawa et al. 2012). CMT is an inherited, progressive peripheral neuropathy that affects both motor and sensory nerves and is genetically heterogenous (Rossor et al. 2013). Clinical evaluations of motor nerve conduction velocities have been used to classify CMT as either demyelinating (type 1) or axonal (type 2). Many individuals with CMT show classic auditory neuropathy

characterized by normal OHC function but significant decreases in hearing sensitivity, often with ABR latency alterations (Rance 2005). Nonetheless, evaluation of a cohort of children genetically diagnosed with CMT1 or CMT2 showed that a majority of cases exhibited decreased speech understanding and altered temporal processing despite normal or near normal auditory thresholds (Rance et al. 2012). Similarly, a recent study of individuals diagnosed with CMT1A, the most common form of CMT that is associated with copy number variation of the gene encoding Peripheral Myelin Protein 22 (*PMP22*), provided additional evidence of HHL in this patient population (Choi et al. 2018). A cohort of 43 CMT1A patients ranging in age from 14 to 64 years showed normal pure tone threshold averages at a range of frequencies (250 Hz to 8 kHz), and their speech perception scores in quiet matched those of a group of age- and sex-matched controls. However, the mean score for speech perception in noise was reduced in the CMT1A patients, and their abilities to detect stimuli that require temporal and spectral acuity were also decreased. Early evaluation of auditory function in mouse models of CMT1 indicated a combination of elements of both HHL and auditory sensitivity defects associated with decreased AN myelination, including loss of AN proximal fibers and SGNs along with small increases in ABR thresholds and large decreases in peak I amplitudes in response to suprathreshold sounds (Zhou et al. 1995). Therefore, it is likely that HHL is an integral part of CMT pathology, whereas the degree of AN demyelination and SGN death dictates whether threshold shifts will be detected in audiometric tests.

Ototoxicity

High doses of aminoglycoside antibiotics such as gentamicin have long been known to cause auditory threshold shifts because of hair cell toxicity (Schacht et al. 2012). Interestingly, this type of exposure also has been shown to induce acute swelling of SGN terminal dendrites (Duan et al. 2000), similar to the morphology associated with excitotoxic damage of IHC synapses by noise exposure (Ruel et al. 2007). Most relevant to the focus of this review, doses of aminoglycosides that spare hair cells also have been linked to loss of IHC synapses, although the precise relationship to HHL and temporal processing in this case has not yet been determined. Liu et al. (2015) reported that systemic delivery of low dose gentamycin to mice for 2 weeks results in a temporary decrease in IHC synapse numbers, which partially recovered following cessation of the drug and suggested that synapses can be restored under these conditions. Oishi et al. (2015) found that a single middle ear administration of low amounts of gentamycin into mice results in small threshold increases associated with both synapse loss and SGN loss while sparing hair cells. This effect was observed although only in XBP-1 mutant mice with compromised stress responses but not in wild-type mice. Additional studies in mice have also implicated systemic gentamycin in acute losses of SGN dendrites (Ruan et al. 2014) or IHC synapses (Hong et al. 2018) at doses that did not cause substantial hair cell loss. In the latter study, synapse loss was accompanied by both small threshold shifts and large declines in ABR peak I amplitudes (Hong et al. 2018).

MECHANISMS OF HIDDEN HEARING LOSS

Cochlear Synaptopathy

The best documented mechanism for HHL is the degeneration of cochlear ribbon synapses without hair cell loss and SGNs (i.e., cochlear synaptopathy) (Fig. 1). These synapses, located at the basal end of IHCs, consist of a presynaptic specialization known as a "ribbon" that contains neurotransmitter vesicles and the release apparatus, as well as a postsynaptic zone in the nerve terminal with AMPA glutamate receptors (Reijntjes and Pyott 2016). The association between HHL and the loss of IHC-SGN synapses was first noted in studies of the effects of moderate noise in mice by Kujawa and Liberman (2009). These TTS exposures resulted in no loss of hair cells and full recovery of auditory thresholds but a permanent decline in AN responses to suprathreshold sounds as measured by the amplitudes of ABR peak I, or of CAPs measured at the cochlear round window. The

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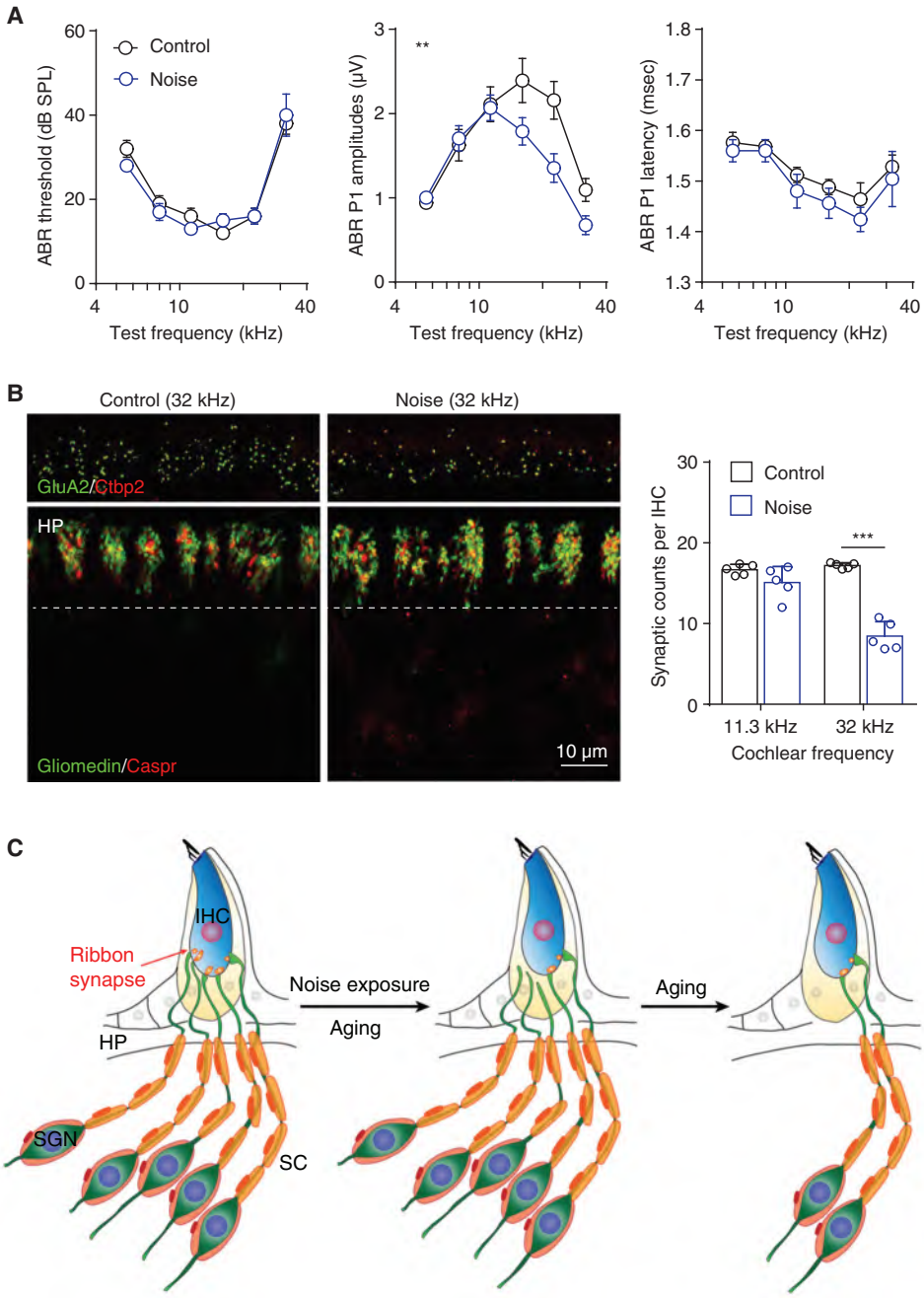

Figure 1. Hidden hearing loss (HHL) caused by cochlear synaptopathy. (*A*) Auditory brainstem response (ABR) recordings of control mice and mice 2 weeks after noise exposure (8–16 kHz, 100 dB sound pressure level [SPL], 2 hours). Noise exposure causes reduction of ABR peak I (P1) amplitudes without changes in threshold and latency. (*B*) The same HHL-causing noise exposure used in *A* results in inner hair cell (IHC) ribbon synapse loss in the base of the cochlea (e.g., 32 kHz region of the cochlea) but does not affect node of Ranvier structures. (*C*) Model for HHL caused by cochlear synaptopathy. Noise exposure or aging result in synaptic degeneration of low spontaneous rate (SR) AN fibers, which over time progresses to spiral ganglion neuron (SGN) loss. (Panels *A* and *B* modified from Wan and Corfas 2017; courtesy of Creative Commons Attribution 4.0 International License.)

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suprathreshold changes were associated with permanent decreases of up to 50% of the number of presynaptic ribbon synapses as determined by immunostaining for RIBEYE/CtBP2, a component of the presynaptic ribbon. The decline in synapse numbers in this study was proportional to the relative decreases in suprathreshold responses and was found in basal, high-frequency regions of the cochlea that showed functional deficits. It has been speculated that the initiator of synapse damage and deafferentation may be glutamate-mediated excitotoxicity, which induces swelling of the SGN terminal fibers under IHC soon after damaging noise exposures (Ruel et al. 2007; Liberman and Kujawa 2017).

Similar characteristics of synaptopathy have also been shown in several mouse strains, and in rats, guinea pigs, chinchillas, and rhesus monkeys following TTS-type noise (Hickox et al. 2017; Valero et al. 2017). Not surprisingly, exposure to higher intensity noise that induces permanent threshold shifts (PTSs) associated with extensive OHC death and moderate IHC losses results in an even greater decrease in synapse numbers on surviving IHC relative to TTS noise exposure (Valero et al. 2017). Although evidence of TTS noise effects in mouse supports the permanence of the synaptic loss (Fernandez et al. 2015), most studies in other species have not examined longer-term effects of noise on synapse integrity. Several recent studies of guinea pigs exposed to less intense noise levels and evaluated at later time points suggest, however, that some synaptic repair may be possible following the initial damage (Liu et al. 2012; Shi et al. 2013, 2015, 2016; Song et al. 2016). As most studies used immunostainings of synaptic markers as indicators of synaptic integrity, it remains to be determined whether synaptic loss and regeneration involves structural alterations and/or dynamic changes in marker expression.

Most of the synapse loss following TTS noise exposure occurs within hours of the noise and appears to preferentially occur in synapses associated with AN fibers that have low spontaneous rate firing activity (low SR) and high threshold response properties (Furman et al. 2013; Liberman and Liberman 2015). These low SR fibers also show larger dynamic ranges (Schalk and Sachs 1980), preserve information concerning stimulus timing and amplitude modulation (AM) more efficiently (Joris et al. 1994; Rhode and Greenberg 1994; Frisina et al. 1996), and are less vulnerable to masking in background noise than high SR fibers (Costalupes et al. 1984). Preferential loss of low SR fibers would therefore be consistent with the decreased responses to suprathreshold sounds and auditory acuity in complex listening environments that have been associated with the synaptic damage from TTS noise exposures. The synapses associated with high SR fibers that remain following TTS noise retain normal threshold and frequency tuning characteristics and presumably explain the recovery of normal auditory thresholds (Furman et al. 2013).

A strong correlation between synapse loss and reduced suprathreshold responses was found in mice during aging, supporting the notion that synaptopathy is a key contributor to progressive auditory neuropathy and HHL in the absence of noise overexposure (Sergeyenko et al. 2013). In addition, SGN loss in aging mice occurred at approximately the same rate as the synaptopathy but with several months delay, suggesting that synapse loss predisposes neurons to degeneration (Sergeyenko et al. 2013). Indeed, mice with noise-induced synaptopathy in the cochlear base at early ages show higher degrees of SGN loss later in life than nonexposed mice, and this occurs in the same cochlear regions affected by the exposure (Fernandez et al. 2015). Electrophysiological studies in aging gerbils indicate that, as in TTS noise-exposed mice, low SR AN fibers are preferentially lost, and supports the idea that loss of such fibers could give rise to the suprathreshold response and temporal coding deficits associated with HHL during aging (Schmiedt et al. 1996).

SGN counts of a large set of human cochleae from a range of subject ages with relatively intact hair cell numbers and no evidence of otologic disease indicated a similar rate of SGN loss across the life span (Makary et al. 2011). In addition, immunostaining for IHC ribbon synapses and peripheral AN fibers in separate sets of human cochleae with relatively intact IHC populations suggested a progressive deafferentation that proceeds faster than the rate of SGN

loss in the Makary et al. study (Viana et al. 2015; Wu et al. 2018). These findings are similar to those obtained in aging mice, suggesting that synaptopathy in humans may also predispose SGN to degeneration.

Demyelination

Proper development and maintenance of AN myelination by Schwann cells is critical for auditory processing fidelity and defects in myelination have been implicated in hearing loss in both humans and animal model systems (Long et al. 2018). Schwann cells are critical for the formation of nodes of Ranvier, the specialized regions along myelinated fibers at which voltage-gated sodium and potassium channels are clustered for regeneration of action potentials and the fast, synchronized transmission of electrical signals (Rasband and Peles 2015). In addition to demyelinating disorders such as CMT1 that clearly affect temporal processing in AN, other risk factors for HHL such as noise and aging have also been associated with myelin dysfunction. Exposure of rats to loud noise has been associated with thinning of myelin surrounding AN and also changes to paranodal myelin regions that are important for function of the nodes of Ranvier (Tagoe et al. 2014). Although this noise level produced increases in threshold shifts, reductions in ABR peak I amplitudes and increases in latency were also observed. Similar myelin defects and changes to suprathreshold stimuli have also been observed in mice exposed to noises that produce a combined TTS-PTS (Panganiban et al. 2018). Other studies based on electron microscopy reported thinning and degeneration of myelin sheaths in the AN of aging mice, which correlated with decreases in myelin basic protein (MBP) levels and declines in ABR peak I amplitudes (Xing et al. 2012). Age-associated decreases in MBP levels were also noted in AN from a set of human temporal bone specimens (Xing et al. 2012), suggesting myelin loss could contribute to the temporal processing abnormalities described in aging humans, including increases in response latency and dyssynchrony (Plack et al. 2014; Harris and Dubno 2017).

Recently, Wan and Corfas (2017) reported that transient demyelination also results in HHL (Fig. 2). This study showed that ablation of Schwann cells via genetic means in adult animals causes a near total loss of AN myelin within 1 week. Remarkably, this loss does not alter auditory thresholds, yet induces a permanent HHL, that is, suprathreshold ABR peak I amplitudes are significantly decreased. In contrast to the HHL produced by noise exposure, ABR peak I latency was also increased by demyelination. These alterations persist even after complete AN remyelination through proliferation and differentiation of new Schwann cell precursors. Although no changes in IHC-SGN synapses were observed following the acute demyelination, immunostaining studies showed a permanent defect in the nodal structures closest to the IHCs, known as heminodes. Electrophysiological and immunostaining studies showed that the heminode is the action potential generator in AN (Hossain et al. 2005; Rutherford et al. 2012; Kim and Rutherford 2016). Together, these observations indicate that heminode disruption is likely to be the basis for the HHL observed following transient demyelination (Wan and Corfas 2017). The temporary hearing sensitivity deficits, together with persistently increased ABR latencies observed in some humans with transient demyelination caused by GBS, appear to match the phenotype of this mouse model (Takazawa et al. 2012).

Hair Cell Dysfunction

Two recent studies suggested that noise-induced hair cell dysfunction could also contribute to HHL. Mulders et al. (2018) reported that guinea pigs with noise-induced HHL also have persistent reductions in summating potential (SP) amplitudes. As the SP reflects the sound-induced IHC receptor current (Zheng et al. 1997), the investigators suggested that long-lasting changes in IHC electrophysiological function might contribute to HHL. However, this finding contradicts other studies in which the SP was reported to be stable after noise exposure in HHL mouse models (Kujawa and Liberman 2009) and during aging (Sergeyenko et al. 2013). The second study involved human listeners and suggested OHC

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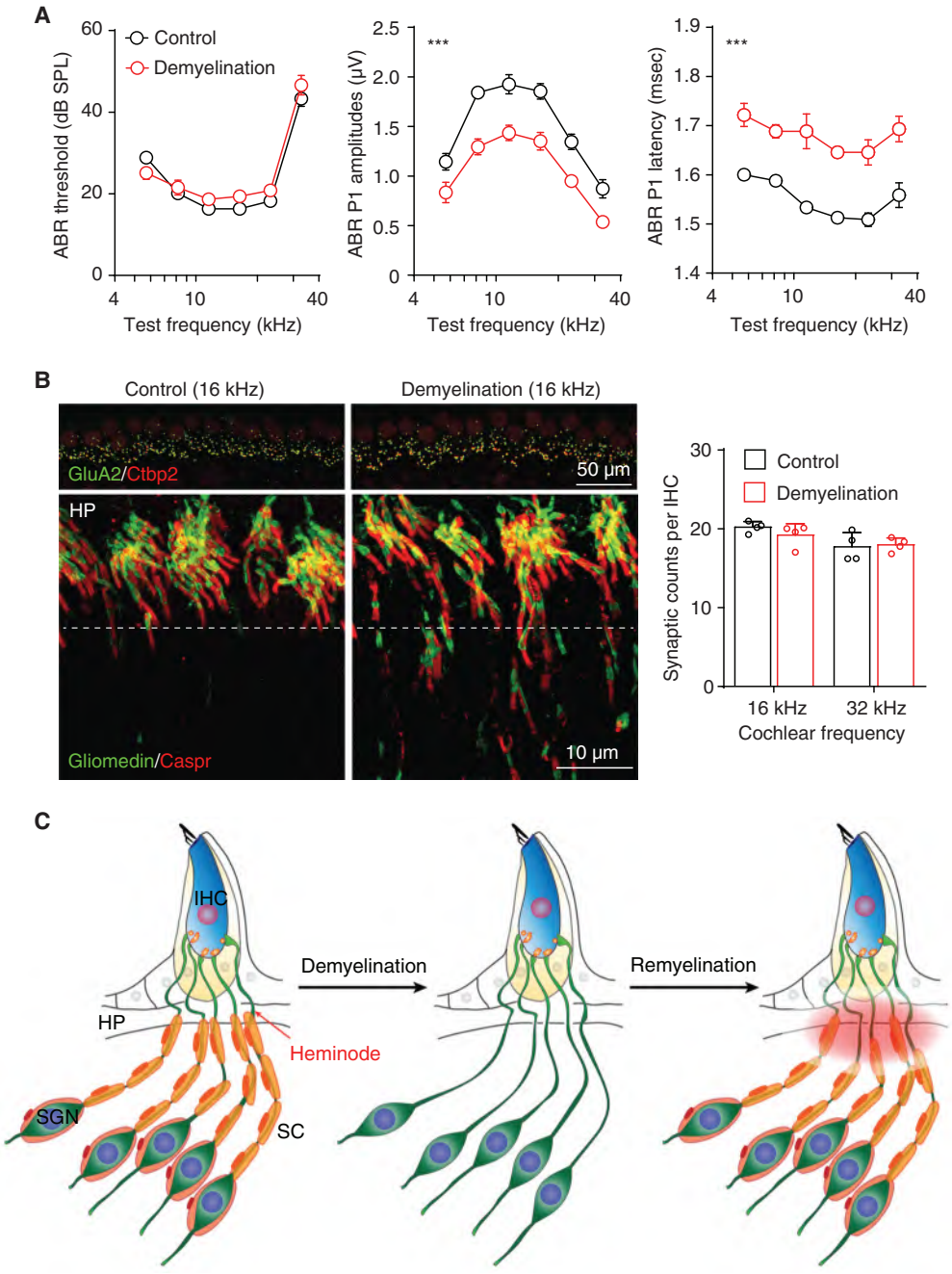

Figure 2. Hidden hearing loss (HHL) caused by cochlear demyelination. (*A*) Auditory brainstem response (ABR) recordings from control mice and mice 4 months after transient demyelination caused by Schwann cell ablation. Mice present with clear signs of HHL, that is, ABR P1 amplitude reduction, latency increase, but no threshold elevation. (*B*) Demyelination causes persistent heminode pathology without loss of ribbon synapses. (*C*) Model for HHL caused by transient demyelination. After auditory nerve (AN) demyelination, remyelination takes place but the heminode structures do not recover. (Panels *A* and *B* modified from Wan and Corfas 2017; courtesy of Creative Commons Attribution 4.0 International License.)

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involvement in HHL (Hoben et al. 2017). This group reported correlations among very mild threshold elevations, altered DPOAEs, and difficulties in speech in noise. Importantly, they found no correlation of those variables with CAP amplitudes. Based on these observations, the investigators hypothesized that loss of OHCs results in sound-induced deflection of a broader region of the basilar membrane, thereby recruiting a larger population of AN fibers and compensating for decreased cochlear amplifier function at low sound levels (i.e., normal CAP thresholds), but that this process leads to altered temporal acuity and compromises speech understanding in noisy backgrounds (Hoben et al. 2017). Further exploration of the contribution of hair cell dysfunction to HHL is necessary.

DIAGNOSIS OF HIDDEN HEARING LOSS

Although HHL can be effectively studied in animal models with a combination of invasive physiological and histological tests, this is not possible in human subjects. Therefore, specific, sensitive, and reliable noninvasive diagnostic tests are essential. Such tools will facilitate studies aimed at understanding the prevalence and natural history of HHL, identifying the specific etiologies responsible for the disease in each patient, and eventually validating therapeutic interventions for this disorder. Below, we summarize several of the diagnostic approaches that are currently being studied in human subjects (see Fig. 3). Yet, is important to note that a controversy still exists whether HHL occurs in humans. Further comparisons between animal models and humans, and larger reference samples from humans will be necessary to establish strong and reliable diagnostic tools. For additional details and discussion of human auditory testing approaches with respect to HHL, see also other recent reviews (Bharadwaj et al. 2014; Plack et al. 2016; Kobel et al. 2017).

ABR Measurements

The most frequently applied tests for HHL are based on ABR recordings and electrocochleograms, with analysis of specific features of the

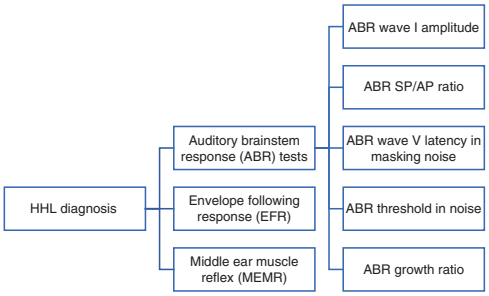

Figure 3. Noninvasive diagnosis of hidden hearing loss (HHL) in rodents and humans. Auditory brainstem response (ABR), envelope following response (EFR), and middle ear muscle reflex (MEMR) recordings are the primary assays for HHL diagnosis. Alterations in the pattern of ABR traces can be used for differential diagnosis of HHL, including peak I amplitude, summating potential (SP)/ABR peak I (AP) ratio, peak V latency in masking noise, threshold in noise, and slope of the sound intensity to peak I amplitude relationship.

waveforms. It has been well documented in animal models that HHL can be diagnosed by a characteristic reduction in ABR peak I amplitudes in the absence of ABR threshold or latency changes (for review, see Hickox et al. 2017). Importantly, the degree of peak I amplitude reduction correlates well with the degree of cochlear synaptopathy (Kujawa and Liberman 2009; Sergeyenko et al. 2013; Wan et al. 2014). Interestingly, mouse studies indicate that demyelination-related HHL has the additional phenotype of increased ABR peak I latency (Wan and Corfas 2017). Similarly, in humans, both aging and noise exposure have been associated with reduction of ABR peak I suprathreshold amplitudes in the absence of threshold changes (Konrad-Martin et al. 2012; Stamper and Johnson 2015). However, unlike in animal models, ABR peak I amplitudes recorded from human subjects are much smaller and more variable, limiting their clinical application for routine HHL diagnosis in individual patients (Beattie 1988; Lauter and Loomis 1988; Trune et al. 1988).

Several studies have used alternative measurements of ABRs or electrocochleography in an attempt to more accurately evaluate AN activity, particularly in humans, to relate changes in these measurements with performance on au-

ditory tasks that rely on precise neural coding of sound. For example, the ratio between ABR peak I (AP) and SP amplitudes (AP/SP ratio) correlates with performance in a test for word comprehension in noise and self-reporting of noise exposure (Liberman et al. 2016). Similarly, latencies of peak V, which is generated by processing in the auditory midbrain, show lower degrees of change in background noise in subjects with poorer abilities in binaural discrimination tasks (Mehraei et al. 2016), consistent with modeling predictions for loss of a subset of AN fibers (Verhulst et al. 2013). Comparable changes were also identified in mice exposed to TTS-level noise that induced ABR peak I amplitude changes and loss of IHC synapses, suggesting that ABR peak V latencies in a masking noise may be useful in assessing HHL in humans (Mehraei et al. 2016). Finally, a number of modeling studies have been used to simulate various cochlear hearing defects, including HHL, to better predict how various aspects of auditory waveforms will behave in response to different stimulus conditions, including pure tone thresholds in noisy backgrounds (Ridley et al. 2018) and by suprathreshold sounds (Verhulst et al. 2016). Further model validation in animals with experimentally induced HHL may lead to more precise test approaches in human, including the ability to isolate synaptopathic effects from more overt hearing loss.

Envelope Following Responses

Envelope following responses (EFRs), also called frequency following responses (FFRs), are far-field responses to AM tones that reflect neural activity at multiple locations along the auditory pathway, with relative responsiveness dependent on the AM frequency (Kuwada et al. 2002; Krishnan 2006). The AM tones are sinusoidal and continuous rather than transient as those used in ABR evaluations, and deficits in EFRs have been correlated with reduced signal detection in noise (Dimitrijevic et al. 2004) and in other listening tasks that require detection of timing cues (Ruggles et al. 2011; Bharadwaj et al. 2015). Recent animal studies indicated that declines in EFR responses to modulation frequencies near 1 kHz correlate well with synaptic loss and HHL induced by TTS noise and by aging (Shaheen et al. 2015; Parthasarathy and Kujawa 2018). Similarly, in a recent study of humans with normal hearing thresholds, control subjects had better EFRs to a 5 kHz, 85 Hz AM tone in background noise than subjects with suspected HHL, whose EFRs were reduced by the noise (Paul et al. 2017). Furthermore, subjects with prior recreational noise exposure appear to have reduced EFR activity compared with control subjects without noise exposure but similar hearing thresholds (Plack et al. 2014). These comparative human and animal studies support the use of EFR as an assay for cochlear synaptopathy and HHL.

Middle Ear Muscle Reflex

Low SR ANs, which are preferentially affected during cochlear synaptopathy, are also required for the middle ear muscle reflex (MEMR) (Liberman and Kiang 1984; Kobler et al. 1992). The MEMR can reduce the sound-evoked excitation of IHCs by increasing the impedance of the middle ear, thus acting as a signal attenuator to protect the cochlea from damaging sounds. MEMR is measured by monitoring the changes in sound pressure in the ear canal ipsilateral to a probe tone while eliciting the MEMR with a sound in either the ipsilateral or contralateral ear. In mouse models of HHL, elevation of MEMR threshold and reduction in suprathreshold MEMR reflex strength are correlated well with synaptopathy (Valero et al. 2016, 2018). In human subjects with tinnitus and normal audiological thresholds, the presence of HHL was suspected based on their significantly weaker MEMR responses relative to control subjects without tinnitus (Wojtczak et al. 2017). Emerging evidence suggests that MEMR may be more sensitive than the suprathreshold amplitude of ABR peak I as an indicator of moderate synaptopathy (Valero et al. 2018).

POTENTIAL TREATMENTS OF HIDDEN HEARING LOSS

Based on the increasing knowledge of mechanisms that underlie HHL, a number of potential

therapeutic approaches have been proposed and/or tested. To date, these have been based on strategies to repair lost IHC-SGN synapses and to augment efferent feedback responses that offer protection from noise trauma.

Neurotrophins as Potential Therapies for Noise-Induced HHL

There is increasing evidence that the neurotrophins, in particular neurotrophin 3 (NT-3), might have the ability to induce IHC synapse regeneration after HHL-inducing noise exposure (Wan et al. 2014; Cunningham and Tucci 2015). We have shown that the levels of NT-3 expression by cochlear supporting cells regulate the density of IHC synapses during cochlear maturation (Wan et al. 2014). Specifically, NT-3 overexpression in supporting cells results in higher synapse density in the cochlear base and higher auditory sensitivity in the corresponding high frequencies. Correspondingly, reductions in NT-3 expression by supporting cells at early postnatal ages results in decreased IHC synapse density in the cochlear base and a mild high-frequency hearing loss. Most relevant to HHL therapeutics, in this study we showed that NT-3 overexpression in supporting cells does not prevent the synaptopathy and TTS elicited by an HHL-inducing exposure, but IHC synapses and ABR peak I amplitudes recover within 2 weeks after the noise, consistent with NT-3 inducing synaptic regeneration. More recent studies have shown that round window delivery of either NT-3 (Suzuki et al. 2016) or NT-3 plus BDNF (Sly et al. 2016) within 24 hours following noise exposure have the same effects as transgenic NT-3 overexpression. The observation that the neurotrophin treatment worked both in mice (Suzuki et al. 2016) and guinea pigs (Sly et al. 2016) strongly supports the potential efficacy of NT-3 as a therapeutic for HHL (Fig. 4).

Modulation of Efferent Feedback

Olivocochlear efferent fibers originating in the auditory brainstem innervate the cochlea and provide feedback control of cochlear activity by the central nervous system (CNS) (Fuchs and Lauer 2018). Lateral olivocochlear (LOC) efferent fibers synapse with the SGN terminals near IHCs, whereas medial olivocochlear (MOC) efferent fibers target OHCs (Frank and Goodrich 2018). Acetylcholine released by MOC neurons bind and activate OHC nicotinic acetylcholine receptors (nAChRs) comprised of the α9/α10 subunits. Activation of these receptors decrease cochlear amplification. Signaling through LOC alters AN response properties and works in part through dopaminergic signaling (Guinan 2018). A number of studies have implicated both MOC and LOC efferents in cochlear protection from noise damage (for review, see Le Prell et al. 2003; Fuente 2015). Although the majority of these studies evaluated protection from intense noise exposures that result in PTS, several recent studies have evaluated the involvement of efferent responses during aging and in response to moderate noise exposures relevant to HHL.

The Liberman laboratory used a surgical ablation approach in mice to show the importance of MOC efferents for hearing protection from an extended exposure to moderate noise (84 dB for 1 week) (Maison et al. 2013). Specifically, they determined that mice with the selective MOC lesion show larger ABR peak I amplitude declines along with greater decreases in synapses than those with intact MOC efferents. A separate study showed that a lesion that removes ~50% of both MOC and LOC fibers results in accelerated age-related HHL and IHC synapse loss in the absence of overt noise exposure (Liberman et al. 2014). Evaluation of innervation in the surgically treated mice suggested that MOC efferents are most important for synaptic protection in the apical half (lower frequencies) of the cochlea, whereas LOC efferent affects predominately the basal half (higher frequencies). More recently, the Gomez-Casati laboratory explored the role of efferents in noise protection by modulating MOC responses in OHCs using mice carrying either a knockout (KO) allele of the OHC α9 nAChR or a knockin (KI) allele of the receptor that increases its activity (Boero et al. 2018). They reported that, as expected, wild-type mice show HHL and synaptopathy 1 week after exposure to a TTS-type noise (100 dB for 1 hour). In contrast, KO mice with loss of OHC

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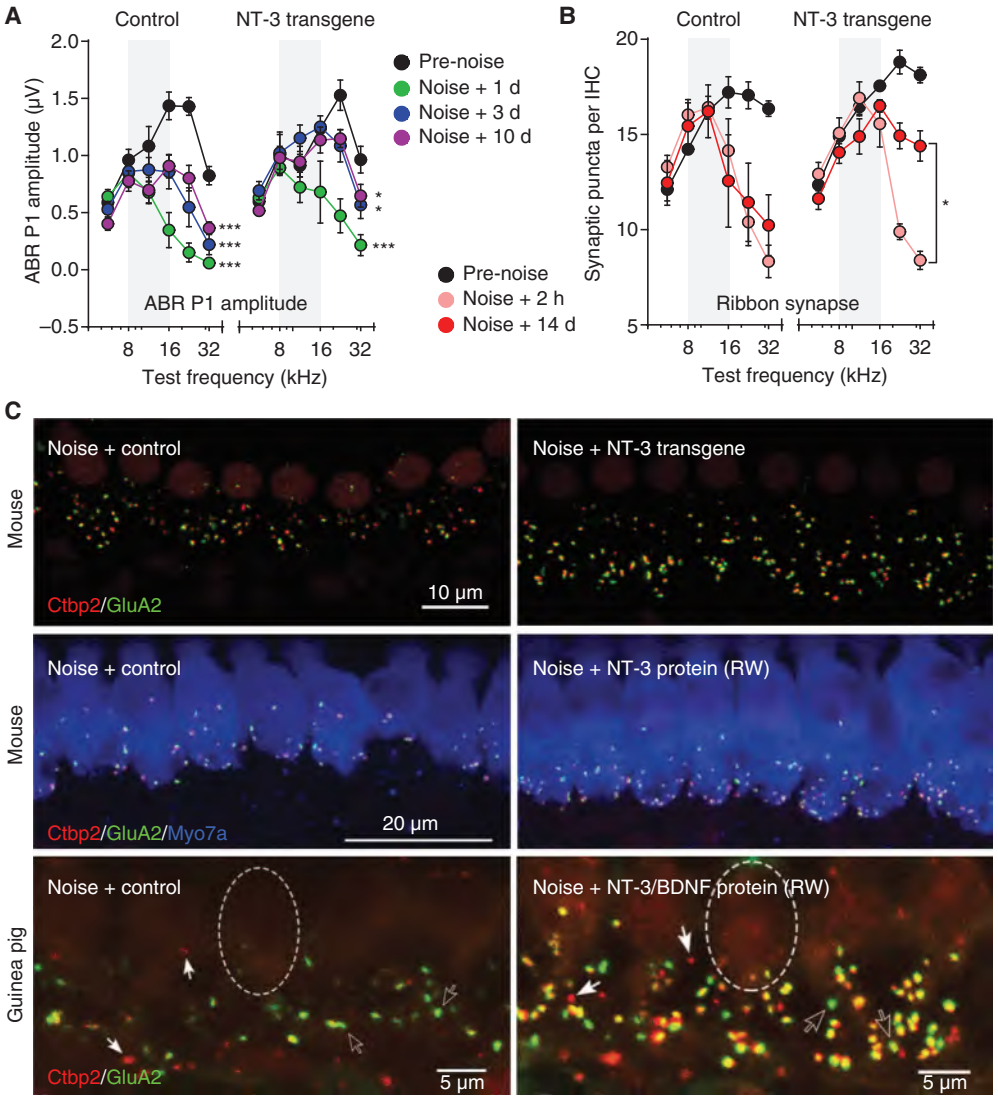

Figure 4. Neurotrophin 3 (NT-3) as a potential therapeutic for treatment of hidden hearing loss (HHL). (*A*) NT-3 transgenic overexpression in adult mouse cochlea promotes recovery of auditory brainstem response (ABR) peak 1 amplitudes after an HHL-inducing noise exposure (8–16 kHz, 100 dB, 2 hours). (*B*) NT-3 transgenic overexpression promotes synaptic regeneration after noise exposure. (*C*) Examples of synaptic immunostainings showing NT-3 transgene or protein promotes synaptic regeneration in both mouse and guinea pig exposed to noise. RW, Round window; inner hair cell (IHC) nucleus, dashed oval; glutamate receptors, black arrows; CtBP2-containing ribbons, white arrows. (Figure panels created from data in Wan et al. 2014, Sly et al. 2016, and Suzuki et al. 2016.)

cholinergic function develop PTS under these conditions, whereas KI mice with enhanced nAChR function do not show signs of HHL. Together, these studies suggest that augmentation of efferent signaling may be a potential strategy for minimizing both HHL resulting from moderate noise exposures, as well as PTS in response to more damaging noise (Maison et al. 2002; Taranda et al. 2009). However, the possibility that the transient MOC connections with IHC that occur during development (Glowatzki and Fuchs 2000; Katz et al. 2004) contribute to these

observations cannot be ruled out. Because LOC effects on IHC-SGN synaptic connections may operate via dopaminergic-mediated mechanisms (Ruel et al. 2001, 2007), it has been speculated that dopaminergic agonists might impact HHL. Along similar lines, NMDA glutamate receptors are expressed by AN fibers and NMDA receptor antagonists have been shown to block AN excitotoxicity (Pujol et al. 1993). Accordingly, a recent report indicated that delivery of the NMDA receptor antagonist esketamine (AM-101) following noise exposure reduces HHL, although postsynaptic integrity was not evaluated in this study (Bing et al. 2015).

CONCLUDING REMARKS

The recent increased awareness of HHL, along with the evidence that synaptopathy is a contributor to noise-induced and age-related hearing loss (Kujawa and Liberman 2009, 2015; Sergeyenko et al. 2013), has created considerable interest among auditory researchers and clinicians. So much so that the terms synaptopathy and HHL sometimes are being used interchangeably. In this review, we have attempted to clarify that other mechanisms in addition to cochlear synaptopathy may also contribute to the pathogenesis of HHL. We believe this information is particularly important when considering how to study HHL in human subjects and will impact both diagnosis and future treatment. For example, detecting reductions in amplitudes of the auditory responses does not necessarily mean the presence of synaptopathy; this finding is also consistent with myelin dysfunction. As of today, the only way to determine the presence of synaptopathy is by histological methods. Ideally, more effective diagnostic tools that distinguish between the different etiologies of HHL in each patient will permit clinicians to define which cochlear component needs to be treated, the synapse, myelin, or hair cells.

The rapid progress in the understanding of the cellular and molecular mechanisms of HHL highlights the possibility that treatments for this pervasive disorder will be available in the foreseeable future. This is important because the disruption in hearing that occurs in HHL is not well treated with current hearing aid and cochlear implant technologies, which principally address deficits in auditory thresholds. There is also a growing sense that HHL can lead to the development of tinnitus (Schaette and McAlpine 2011; Epp et al. 2012) and can contribute to the acceleration of age-related hearing loss (Kujawa and Liberman 2006, 2009; Viana et al. 2015; Wu et al. 2018). Thus, finding treatments for HHL could have impact on other prevalent hearing disorders. Furthermore, because hearing loss is a significant risk factor for cognitive decline and dementia (Livingston et al. 2017; Loughrey et al. 2018), timely management of HHL may reduce the incidence of both permanent hearing loss and dementia in the elderly population.

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Auditory Brainstem Response Altered in Humans With Noise Exposure Despite Normal Outer Hair Cell Function

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Abstract

Objectives—Recent animal studies demonstrated that cochlear synaptopathy, a partial loss of inner hair cell-auditory nerve fiber synapses, can occur in response to noise exposure without any permanent auditory threshold shift. In animal models, this synaptopathy is associated with a reduction in the amplitude of wave I of the auditory brainstem response (ABR). The goal of this study was to determine whether higher lifetime noise exposure histories in young people with clinically normal pure-tone thresholds are associated with lower ABR wave I amplitudes.

Design—Twenty-nine young military Veterans and 35 non Veterans (19 to 35 years of age) with normal pure-tone thresholds were assigned to 1 of 4 groups based on their self-reported lifetime noise exposure history and Veteran status. Suprathreshold ABR measurements in response to alternating polarity tone bursts were obtained at 1, 3, 4, and 6 kHz with gold foil tiptrode electrodes placed in the ear canal. Wave I amplitude was calculated from the difference in voltage at the positive peak and the voltage at the following negative trough. Distortion product otoacoustic emission input/output functions were collected in each participant at the same four frequencies to assess outer hair cell function.

Results—After controlling for individual differences in sex and distortion product otoacoustic emission amplitude, the groups containing participants with higher reported histories of noise exposure had smaller ABR wave I amplitudes at suprathreshold levels across all four frequencies compared with the groups with less history of noise exposure.

Conclusions—Suprathreshold ABR wave I amplitudes were reduced in Veterans reporting high levels of military noise exposure and in non Veterans reporting any history of firearm use as compared with Veterans and non Veterans with lower levels of reported noise exposure history. The reduction in ABR wave I amplitude in the groups with higher levels of noise exposure cannot be accounted for by sex or variability in outer hair cell function. This change is similar to the decreased ABR wave I amplitudes observed in animal models of noise-induced cochlear

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synaptopathy. However, without post mortem examination of the temporal bone, no direct conclusions can be drawn concerning the presence of synaptopathy in the study groups with higher noise exposure histories.

Keywords

Auditory brainstem response; Auditory nerve; Cochlear neuropathy; Cochlear synaptopathy; Hidden hearing loss; Noise-induced hearing loss; Veterans

INTRODUCTION

The two most common service-related disabilities experienced by Veterans, hearing loss and tinnitus, are frequent consequences of exposure to high intensity noise. Over 2 million Veterans received service-connected disability compensation benefits for hearing loss or tinnitus in 2014 (Veterans Benefits Administration 2014). In addition to military personnel, in the United States, an estimated 30 million people are exposed to hazardous noise levels at work (National Institute for Occupational Safety and Health 1998) and many more are exposed to hazardous noise during recreational activities. For decades, scientists assumed that outer hair cell (OHC) death was the primary indicator of noise-induced hearing loss and tinnitus. However, recent animal studies demonstrated that noise exposure can permanently damage auditory nerve fibers, even when hair cell function recovers and there is no permanent threshold shift (Kujawa & Liberman 2009; Lin et al. 2011). In mice, initial loss of auditory nerve synapses onto inner hair cells (IHCs), which occurs primarily during the 2-hr noise exposure (Liberman et al. 2015), is followed by a slower degeneration of the spiral ganglion cell bodies over the course of several months to years (Kujawa & Liberman 2009). In mice, degeneration of the IHC-auditory nerve synapse occurs not only in response to noise exposure but also with aging (Sergeyenko et al. 2013).

Previous studies in mice, gerbils, and guinea pigs showed that the amplitude of wave I of the auditory brainstem response (ABR) is correlated with the number of IHC synaptic ribbons and spiral ganglion cell bodies, with smaller amplitudes found in animals with partial loss of auditory nerve fibers (Kujawa & Liberman 2009; Earl & Chertoff 2010; Lin et al. 2011; Sergeyenko et al. 2013; Fernandez et al. 2015). Wave I of the ABR is a small far-field response produced by the combined synchronous firing of numerous auditory nerve fibers (Hashimoto et al. 1981; Møller & Jannetta 1981). Age-related reduction in ABR wave I amplitude has been demonstrated in humans (Konrad-Martin et al. 2012) and is consistent with temporal bone studies showing auditory neuronal and synaptic loss with age (Makary et al. 2011; Viana et al. 2015). In addition, Stamper and Johnson (2015a) found weak evidence of a relationship between ABR wave I amplitude and self-reported noise exposure over the previous year in young adults with normal pure-tone thresholds, with smaller amplitudes for individuals with greater reported noise exposure. However, a follow-up analysis showed that this relationship only held true for females and not for males (Stamper & Johnson 2015b).

Auditory nerve fibers can be divided into subpopulations based on their spontaneous firing rate (low versus high) with low spontaneous rate fibers exhibiting high thresholds, whereas high spontaneous rate fibers exhibit low thresholds (Liberman 1978). The range of

thresholds enables the auditory system to respond to sounds over a large dynamic range. Low spontaneous rate fibers seem to be the most vulnerable to noise exposure (Furman et al. 2013). A study in gerbil showed that low spontaneous rate fibers may also be more vulnerable to aging than other subpopulations of fibers (Schmiedt et al. 1996). When low spontaneous rate fibers are missing, thresholds are unaffected because high spontaneous rate fibers respond to the sound (Furman et al. 2013). For this reason, the loss of cochlear synapses associated with noise exposure or aging has been termed “hidden hearing loss” because it is not detected on a standard clinical audiogram. Although the perceptual consequences of hidden hearing loss are still unclear, potential impacts that have been proposed include tinnitus, hyperacusis, and difficulty understanding speech in background noise (Schaette & McAlpine 2011; Gu et al. 2012; Hickox & Liberman 2014; Bharadwaj et al. 2015; Bramhall et al. 2015; reviewed in Kujawa & Liberman 2015). Therefore, it is important to verify whether humans are affected by noise-induced hidden hearing loss so that the prevalence of this condition and the effects on auditory perception can be determined.

In this study, suprathreshold ABR wave I amplitude, distortion product otoacoustic emissions (DPOAEs), and self-reported lifetime noise exposure history were evaluated in young military Veterans and non Veterans with normal pure-tone thresholds. Given that direct confirmation of cochlear synaptopathy requires examination of the temporal bone (Viana et al. 2015), ABR wave I amplitude was used as an indirect measure of cochlear synaptic health. Veterans who reported the highest levels of noise exposure during their military service showed reduced ABR wave I amplitudes at all frequencies tested (1, 3, 4, and 6 kHz) compared with Veterans and non Veterans with less reported noise exposure, even after accounting for individual differences in OHC function as measured by DPOAEs. In addition, non Veterans with a history of firearm use also showed a decrease in ABR wave I amplitude compared with non Veterans who had never used firearms. As an indirect measure of cochlear synaptopathy, it is possible that ABR wave I amplitude could also be influenced by damage to IHCs or the auditory nerve or OHC dysfunction not reflected in the DPOAE measures. Therefore, noise-related reductions in ABR wave I amplitude should be interpreted with caution at this time.

MATERIALS AND METHODS

Participants

One Hundred participants ages 19 to 35 were screened for this study. Participants were recruited from previous studies conducted at the National Center for Rehabilitative Auditory Research and by posting fliers at the Portland VA and Portland area colleges and universities. All participants received an audiometric evaluation from a licensed audiologist including tympanometry, air and bone conduction thresholds, and a screening of DPOAE levels in response to moderate level stimuli. All participants were in good general health with no significant history of otologic or neurologic disorder (including traumatic brain injury). Only participants with normal tympanograms (peak pressure ±50 daPa for a 226 Hz tone, compliance between 0.3 and 1.3 ml), no air-bone gaps greater than 15 dB and no more than one air-bone gap equal to 15 dB, normal pure-tone thresholds (no audiometric

thresholds poorer than 20 dB HL from 0.25 to 8 kHz), no evidence of a noise notch (threshold at 1 or 2 frequencies between 3 and 6 kHz that is 15 dB or poorer than the adjacent frequencies), and normal DPOAEs from 1.5 to 6 kHz (compared with published normative values [Gorga et al. 1997, Table A1]) were included. These inclusion criteria were designed to limit the degree of OHC loss in participants, making it easier to evaluate neural changes resulting from noise exposure. Thirty-six participants were excluded from the study after the screening evaluation for the following reasons: poor audiometric thresholds (4), abnormal tympanograms (6), low DPOAE levels (16), history of traumatic brain injury (3), and reported history of significant noise exposure for non Veterans (3). Four participants withdrew from the study before completing testing. A total of 64 participants were enrolled in the study (16 Veterans with a significant history of noise exposure, 13 Veterans with less noise exposure, 12 non Veterans with a history of firearm use, and 23 non Veterans without firearm use). After the screening evaluation, all subsequent study measures were taken only in a single ear. If only one ear met the study criteria (based on audiometric air and bone conduction thresholds, DPOAE screening, and tympanometry), that ear was tested. Thirty-four subjects qualified for the study only in a single ear (11 Veterans with high noise exposure, 7 Veterans with low noise exposure, 4 non Veterans with firearm use, and 12 non Veterans without firearm use). If both ears qualified for the study, the ear with higher level DPOAEs was tested to minimize the effects of OHC loss.

Procedures

All study procedures were approved by the Institutional Review Board of the VA Portland Health Care System.

Audiometric Testing—Pure-tone thresholds for the standard audiometric frequencies (0.25 to 8 kHz) were assessed in all potential participants as part of the screening evaluation. In addition, audiometric thresholds from 9 to 16 kHz were measured in 38 of 64 qualifying participants using Sennheiser HDA 200 headphones (Old Lyme, CT).

Electrophysiological Testing—Electrophysiological testing was completed using an Intelligent Hearing Systems SmartEP system (Miami, FL) and Etymotic Research gold foil ER3-26A tiptrode electrodes (Elk Grove Village, IL) placed in the ear canal. The reference electrode was placed on the high forehead and the ground on the low forehead. Waveforms were generated using alternating polarity toneburst stimuli presented at 5 levels at 1 kHz (70, 80, 90, 100, and 110 dB peak to peak equivalent SPL [dB p-pe SPL]), 6 levels at 4 kHz (60, 70, 80, 90, 100, and 110 dB p-pe SPL), and at a single level (110 dB p-pe SPL) at 3 and 6 kHz. Stimulus durations were 4 msec for 1 kHz (4 cycles), 2.5 msec for 3000 Hz (7.5 cycles), 2 msec for 4 kHz (8 cycles), and 1.5 msec (9 cycles) for 6 kHz. These stimulus durations were chosen as a compromise between frequency specificity and stimulus brevity. All stimuli had a rise/fall time of 0.5 msec and a Blackman envelope. The ABR response was band-pass filtered from 10 to 1500 Hz and averaged across 2048 stimulus presentations for levels of 60 to 100 dB p-pe SPL to increase the signal to noise ratio and across 1024 presentations at 110 dB p-pe SPL due to the high stimulus level. A stimulus repetition rate of 11.1/s was used and two replications of each waveform were obtained. Electrode impedance was less than 5 kOhms, with the exception of 2 participants who had impedance

values of less than 12 kOhms. Positive peaks and the following negative troughs for waves I, III, and V were initially identified with an automated Python-based peak picking program (adapted from Buran 2015). Peaks and troughs were then evaluated by an experienced audiologist and reassigned if necessary. Wave amplitudes for waves I and III were defined as the difference between the voltage at the positive peak and the voltage at the following negative trough. Due to difficulty identifying the wave V trough by both the peak picking program and the audiologist, the amplitude of wave V was calculated as the difference between the peak voltage and the average prestimulus baseline voltage calculated for the 1-msec time period before stimulus presentation. ABR wave I was identified at the 110 dB p-pe SPL stimulus level for all participants in response to tonebursts at 3, 4, and 6 kHz. However, wave I could not be identified at this level in 6 participants at 1 kHz. Waves III and V were identified in all participants for a 4 kHz stimulus at 110 dB p-pe SPL.

Otoacoustic Emissions Testing—DPOAE testing was conducted using a custom system that includes an ER-10 B+ probe microphone and EMAV software from Boys Town National Research Hospital (Neely & Liu 1993). As part of the screening for study candidacy, DPOAE stimuli were presented at a fixed primary frequency ratio $f_1/f_2 = 1.2$ and responses were obtained using a primary frequency sweep (DP-gram) from 1.5 to 6 kHz in 1/6-octave increments at stimulus frequency levels of $L_1 = 65$ and $L_2 = 55$ dB SPL. Responses were compared with the DPOAE levels at the 90th and 95th percentile from a distribution of individuals with abnormal pure-tone thresholds (Gorga et al. 1997, Table A1). Only individuals at or above the 90th percentile at all tested frequencies and below the 95th percentile at no more than one tested frequency were included in the study.

DPOAE input/output (I/O) functions were obtained at 1, 3, 4, and 6 kHz. Primary tones had a fixed primary frequency ratio (f_1/f_2) of 1.3 to decrease the likelihood of suppression effects by L_1 on f_2 and L_2 on f_1 (Withnell & Yates 1998). The level of f_1 was held constant at 70 dB SPL, while the level of f_2 was varied from −5 to 80 dB SPL, similar to the paradigm described by Withnell and Yates (1998) to estimate basilar membrane response growth from DPOAE measurements in guinea pigs. Measurement-based stopping rules were employed in which averaging continued until 30 seconds of artifact-free data were collected or until the noise floor was below −15 dB SPL. The maximum DPOAE level was extracted from the I/O function at each frequency to provide a frequency-specific estimate of OHC function for each participant.

Assessment of Noise Exposure History—All potential participants were asked several questions about their lifetime noise exposure history (occupational, military, and recreational) and use of hearing protection during a short interview. The responses to these questions were used to determine whether potential non Veteran control participants should be excluded based on their level of previous noise exposure and to assign Veterans to the Low or High Noise group. The noise exposure history interview questions and details of how the responses were used to make group assignments can be found in the supplemental data (see Supplemental Digital Content 1, http://links.lww.com/EANDH/A308). The determinations made based on the noise exposure history interview were reassessed and adjusted if necessary after obtaining the results of the Lifetime Exposure of Noise and

Solvents Questionnaire (LENS-Q; Griest, Reference Note 1). This in-depth questionnaire asks about the frequency and duration of exposure, as well as the use of hearing protection for a large variety of possible sources of noise exposure across three categories: nonmilitary occupational noise, military occupational noise, and nonoccupational/recreational noise. Sample questions from the LENS-Q can be found in the supplemental data (see Supplemental Digital Content 1, http://links.lww.com/EANDH/A308). Participants were recruited for three noise exposure groups (Veterans with high noise exposure history, Veterans with low noise exposure history, and non Veteran controls), but 12 non Veteran participants who did not report firearm use during their noise exposure interview reported firearm use on the LENS-Q after they had been enrolled in the study. Due to the high intensity of noise exposure associated with firearm use, we felt it was inappropriate to include these participants in the non Veteran control group. This resulted in the creation of a fourth group, non Veterans with a history of firearm use. The LENS-Q was completed by all non Veteran participants, but only by 15 Veterans (7 assigned to the Veteran High Noise group and 8 assigned to Veteran Low Noise group). The remaining 14 Veterans completed the LENS-Q as part of another study and informed consent could not be obtained to use their LENS-Q data in this study. A summary of the participant characteristics for each noise exposure group is provided in Table 1. Although efforts were made during recruitment to gender balance each noise group, this proved difficult for the non Veteran control and Veteran High Noise groups, which were skewed toward females and males, respectively. The non Veteran control group was skewed toward females in part because more males than females who responded to the study flier reported regular recreational or occupational noise exposure and were not invited to participate in the study. This highlights the importance of adjusting for sex, which is described in the analysis.

The LENS-Q was scored by assigning an intensity value to each noise exposure activity based on publically available databases of noise level measurements (Berger 2015; National Acoustic Laboratories 2015, described in Beach et al. 2013). Most of the available data were measured in dBA, while impulse noise measurements were taken in peak dB SPL. For activities where multiple intensity measurements were publicly available, the mean value of all available measurements was used. This value was then adjusted based on the participant's report of hearing protection use for that activity. The level was reduced by 15 dB for activities where they reported using hearing protection "always," 10 dB for using hearing protection "most of the time," and 5 dB for using hearing protection "some of the time" (based on Berger 2003, details in the supplemental data; see Supplemental Digital Content 1, http://links.lww.com/EANDH/A308). This hearing protection-corrected intensity level was then assigned a weight. Weights began with a value of 1 for an intensity level of 80 dBA and doubled with each 3 dB increase in intensity level (e.g., 80 dBA = 1, 83 dBA = 2, 86 dBA = 4, 89 dBA = 8, etc.). This weight was then multiplied by the reported frequency and duration of exposure, resulting in an overall exposure value for each activity. Exposure values were summed for all reported activities to calculate the raw LENS-Q score. Due to the skewed distribution of the raw scores from the LENS-Q resulting from the high levels of noise exposure experienced by many of the Veterans, the final LENS-Q score was calculated by taking the logarithm of the raw score. Using this scoring system, each integer increase in LENS-Q score indicates a 10-fold increase in noise exposure. A sample LENS-Q score

calculation is included in the supplemental data (see Supplemental Digital Content 1, http://links.lww.com/EANDH/A308).

Analysis

Bayesian regression analysis was used to model the mean ABR wave I amplitude for each combination of level, frequency, and noise exposure group, while adjusting for the possible confounders sex and DPOAE maximum level. This approach also allowed for the modeling of variability among participants who provided repeated measurements across ABR stimulus conditions. Maximum DPOAE levels were used in the analysis rather than pure-tone thresholds because including DPOAE levels specifically accounts for differences in OHC function between participants. In contrast, pure-tone thresholds could be impacted by damage or dysfunction to parts of the auditory system other than OHCs. Bayesian analysis combines prior knowledge about relevant effects with experimental evidence to output a posterior probability distribution about those effects. All inferences, such as confidence intervals, probabilities that effects are greater or less than zero, etc. are deduced from the posterior probability distribution. Bayesian analysis was chosen for this study over more classical statistical methods because it incorporates prior experience with the relevant parameters, permits simple adjustments for multiple measurements collected from each participant, and does not require large sample sizes. As conventional p value concepts do not exist in Bayesian approaches, no p values appear in this analysis. Instead, the probability of a true difference in mean ABR wave I amplitude between noise exposure groups was calculated by comparing the mean wave I amplitude posterior probability distribution across groups.

A total of 64 participants provided 893 identifiable ABR wave I amplitude measurements in response to nine frequency-level stimulus combinations. The measurements were fairly well distributed across study groups, with non Veteran control participants offering the most measurements because wave I was most easily identified across stimulus conditions in that group. A lognormal probability distribution was assumed for the data, given that ABR wave I amplitudes are by definition positive numbers. Based on this assumption, each of the 893 ABR wave I amplitude measurements was modeled as a lognormal random variable with the parameters μ_i (the log median wave I amplitude for the ith stimulus level-frequency combination) and $|\xi|$ (a scaling parameter). The mean wave I amplitude at a particular stimulus level and frequency can be calculated from μ_i by the equation

$$\text{Mean wave I amplitude} = \exp(\mu_i + \xi^2/2). \quad (1)$$

The log median wave I amplitude μ_i was modeled by regression with the stimulus level and stimulus frequency as independent variables, such that

$$\mu_i = \beta_0 + \beta_1 \cdot \left(\frac{\text{level}_i - 100}{10}\right) + \beta_2 \cdot \log_2(\text{freq}_i) + \beta_3 \cdot \left(\frac{\text{level}_i - 100}{10}\right) \cdot \log_2(\text{freq}_i). \quad (2)$$

In this equation, β_0, β_1, β_2, and β_3 are coefficients for the intercept, level, frequency, and level by frequency interaction, respectively. The linear transformation of stimulus level and the $\log_2$ transformation of stimulus frequency were used to facilitate model fitting. The coefficients β_1 and β_2 were expected to be positive, indicating an increase in wave I amplitude as level increases and higher wave I amplitudes for the higher frequencies compared with 1 kHz. The interaction effect β_3 allows the relationship between stimulus level and wave I amplitude to vary as a function of frequency.

Noise exposure group, sex, DPOAE level, and participant-specific variability moderate the intercept, level, frequency, and level by frequency interaction effects. These moderating effects were modeled as random effects, resulting in a hierarchical model centered at Eq. (2). If the experimental data provide little information about the moderating effects (e.g., if there is little evidence of noise exposure group, sex, or DPOAE effects), then the variances of the random effects distributions will be close to zero, and the regression coefficients associated with the group, sex, or DPOAE effects will "shrink" toward the overall level and frequency effects given by β_0, β_1, β_2, and β_3. This results in a fitted model dictated primarily by the coefficients of the intercept, level, frequency, and level by frequency interaction [Eq. (2)]. In this way, the hierarchical model controls against "false discoveries" of important group effects in a manner analogous to, although more easily interpretable than, classical multiple testing corrections, such as Bonferroni (Gelman et al. 2012).

Model parameters (β_0, β_1, β_2, β_3, and the variance components of the hierarchical model) were estimated using a Bayesian approach (Gelman et al. 2013). Bayesian analysis requires a quantitative characterization of pre-experimental expectations about all model parameters, which are referred to as priors. Priors for the model parameters were chosen to correspond to an expected change in ABR wave I amplitude for a 4 kHz stimulus at 100 dB p-pe SPL compared with a 4 kHz stimulus at 110 dB p-pe SPL of approximately 0.15 μV, with 90% certainty that the increase in amplitude with level is less than 2.5 μV. These priors were chosen based on the assumption that wave I amplitude should increase as stimulus level is raised (Jiang 1991). The model was refit using three alternate priors, including one with variances that are roughly four times greater than those expressed above. This sensitivity analysis yielded little impact of the different priors, suggesting that the posterior distribution (probability distribution of the parameters given the priors and the experimental data) of the effects of interest was largely dominated by the experimental data rather than by the priors. A more detailed description of the Bayesian regression analysis can be found in the supplemental data (see Supplemental Digital Content 1, http://links.lww.com/EANDH/A308).

RESULTS

Distribution of LENS-Q Scores

Figure 1 shows the distribution of LENS-Q scores across participants, as well as their final noise exposure group assignment. LENS-Q scores were obtained for 50 out of the 64 participants (LENS-Q data was not available for 14 of the 29 Veterans). The bimodal distribution observed is not unexpected as recruitment was specifically targeted to non Veterans controls with a very limited history of noise exposure and Veterans with a

significant history of noise exposure. All but one of the Veterans who were initially assigned to the Veteran High Noise group based on the noise exposure interview had a LENS-Q score of greater than 15 and all but one of the Veterans assigned to the Veteran Low Noise group had a LENS-Q score of less than 15. Based on this information and the distribution of the LENS-Q scores, Veterans with a score of greater than or equal to 15 were assigned to the Veteran High Noise group and Veterans with a score lower than 15 were assigned to the Veteran Low Noise group. Non Veterans were assigned to the non Veteran Firearms group if they reported any history of firearm use on the LENS-Q, with or without hearing protection. As a result of the LENS-Q findings, 2 of the 15 Veterans were moved from one noise exposure group to the other and 12 of the 35 non Veterans were placed in the non Veteran Firearms group. In Veteran participants, the results from the LENS-Q generally corroborated the results from the noise history interview. However, the LENS-Q discovered additional information regarding firearm use in non Veterans that was not revealed in the interview.

When firearm use was removed from the calculation of the LENS-Q score, the mean scores for the non Veteran Firearms group and the non Veteran control group were very similar. The adjusted mean LENS-Q score was 5.52 (SD = 3.01) for the non Veteran Firearms group versus 4.28 (SD = 2.70) for the non Veteran control group. This indicates that the primary difference in noise exposure between these two groups was a history of firearm use. It is important to note that most participants in the non Veteran Firearms group were not routine users of firearms. In fact, 9 out of 12 (75%) reported using firearms only a few times or less over their lifetime. The remaining three reported using firearms “several times a year” over 5 to 13 years with hearing protection used “most of the time” or “always.” Fifty percent of the participants in this group reported always wearing hearing protection while using firearms.

Pure-Tone Thresholds and DPOAE Levels Were Similar Across Noise Exposure Groups

Due to the screening criteria, all participants had pure-tone thresholds of 20 dB HL or better from 0.25 to 8 kHz. Although the best thresholds in this range were seen in individuals in the non Veteran group and the poorest thresholds in the Veteran High Noise group (Fig. 2A), the difference in mean pure-tone average (average of thresholds at 0.5, 1, and 2 kHz) between these 2 groups was 3.27 dB and the difference in mean high-frequency pure-tone average (average of thresholds at 2, 3, and 4 kHz) was 7.31 dB. Pure-tone thresholds from 9 to 16 kHz also showed no systematic differences in performance between the noise exposure groups (Fig. 2B).

Although DPOAEs were screened in all participants from 1.5 to 6 kHz, I/O functions at 1, 3, 4, and 6 kHz were generated to provide more detailed information about OHC function. Maximum DPOAE levels from the I/O functions were similar across noise exposure groups (Fig. 3), suggesting comparable OHC function. The L_2 corresponding to the maximum DPOAE level was also similar across groups (data not shown).

ABR Amplitudes Were Reduced in the Noise Exposure Groups With the Highest Levels of Noise Exposure for Wave I, But Not Waves III and V

Average ABR waveforms for each exposure group in response to a 4 kHz 110 dB p-pe SPL stimulus are shown in Figure 4A. From this plot, it is clear that the two groups with the least

noise exposure history (non Veteran controls and Veteran Low Noise) had the largest mean wave I amplitudes and the group with the most noise exposure (Veteran High Noise) had the smallest mean wave I amplitude. The mean wave I amplitude for the non Veteran Firearms group was also reduced compared with the mean amplitudes of the lowest noise exposure groups.

In contrast to wave I amplitude, wave III and V amplitudes for a 4 kHz 110 dB p-pe SPL stimulus were similar across noise exposure groups (Fig. 4B). Individual and group mean wave I amplitudes in response to a 4 kHz toneburst at 4 different stimulus levels (80, 90, 100, and 110 dB p-pe SPL) are shown in Figure 5. At 80 dB p-pe SPL, wave I could not be identified for all participants, resulting in less data at that level. At the higher stimulus levels, wave I amplitudes for the Veteran High Noise group were clearly reduced compared with the non Veteran and Veteran Low Noise groups. A decrease in wave I amplitude was also visible in the non Veteran Firearms group at 110 dB p-pe SPL. Interestingly, across stimulus level, there was little difference in wave I amplitude between the non Veteran control group and the Veteran Low Noise group even though the individuals in the Veteran Low Noise group reported more high intensity noise exposure than the non Veteran controls as indicated by the group mean LENS-Q scores.

ABR Wave I Amplitude Differences Between Noise Exposure Groups Persisted Even After Accounting for DPOAE and Sex Differences

A Bayesian regression model was used to model the mean ABR wave I amplitude for each combination of noise exposure group and stimulus frequency/level, while adjusting for the effects of sex and DPOAE maximum level.

Figure 6 compares the fitted Bayesian regression model to the measured ABR wave I amplitudes for each group, frequency, and level. The pale gray lines and circles are the wave I amplitudes measured for each participant. The black dashed line indicates the mean measured wave I amplitudes at each level. The solid red line illustrates the fitted means generated by the model, with the error bars showing posterior 90% Bayesian confidence intervals of the fitted means. The error bars translate to a 90% chance of the true mean wave I amplitude occurring within this interval. The model uses data from all frequency/level combinations tested and provides fitted ABR wave I amplitudes even for frequency/level combinations that were not measured empirically. However, fitted wave I amplitudes are much less precise (i.e., confidence intervals are wider) at the frequency/level combinations where little or no data were collected, such as for 3 and 6 kHz tonebursts at levels below 110 dB p-pe SPL. For this reason, conclusions were drawn only for frequency/level combinations where ABR measurements were taken.

The fitted ABR wave I amplitude means generated by the model are shown in Table 2 for each group and stimulus frequency/level combination. Decreases in mean wave I amplitude are apparent for the higher noise exposure groups (non Veteran Firearms and Veteran High Noise) compared with the lower noise exposure groups (non Veteran and Veteran Low Noise) across frequency, with the largest reductions at the highest stimulus levels.

The differences in fitted mean wave I amplitude between the non Veteran control group and the other 3 noise exposure groups for each frequency at a stimulus level of 110 dB p-pe SPL are plotted in Figure 7. A value of 0 on the *y* axis indicates no difference from the non Veteran control group, while a negative value indicates a decrease in mean wave I amplitude compared with the non Veteran controls and a positive value indicates an increase. The error bars are posterior 90% Bayesian confidence intervals of the fitted mean differences. This plot shows a decrease in mean wave I amplitude for the Veteran High Noise and non Veteran Firearms groups compared with the non Veteran control group across frequency, with the biggest decrease seen in the Veteran High Noise group at 4 kHz. The Veteran Low Noise group shows little difference in mean wave I amplitude compared with the non Veteran control group regardless of frequency. The probabilities that each of the noise exposure groups had a mean wave I amplitude less than the non Veteran control group at each frequency were calculated from the wave I amplitude difference posterior probability distributions and are shown in Table 3. The probabilities for 4 kHz at 110 dB p-pe SPL for the Veteran High Noise, Veteran Low Noise, and non Veteran Firearms groups were 99.05, 64.45, and 94.30% respectively. This is consistent with true decreases in wave I amplitude for the Veteran High Noise and non Veteran Firearms groups, but not the Veteran Low Noise group. The fitted mean wave I amplitude decrease in the Veteran High Noise group at 4 kHz was −0.129 μV and represents a decrease of 29% compared with the non Veteran control group. In comparison, animal studies of noise-induced cochlear synaptopathy have shown wave I amplitude decreases of 40 to 60% in noise-exposed animals (Kujawa & Liberman 2009; Lin et al. 2011).

Effect of Sex on ABR Wave I Amplitude Was Weak

Modeled mean wave I amplitudes for a 4 kHz stimulus at levels of 80 to 110 dB p-pe SPL are compared for males and females from the Veteran High Noise and non Veteran control groups in Figure 8. Females are shown with blue solid lines and males with dashed red lines. The error bars are posterior 90% Bayesian confidence intervals of the fitted means. This figure shows only weak effects of sex on the fitted mean wave I amplitudes of these groups. At 110 dB p-pe SPL, fitted mean wave I amplitude is 0.013 μV (confidence interval = −0.047 to 0.072) greater in females than males in the Veteran High Noise group and 0.018 μV (confidence interval = −0.071 to 0.095) greater in females in the non Veteran group. Note that this difference in mean wave I amplitude between females and males is an order of magnitude smaller than the reduction in mean wave I amplitude for the Veteran High Noise group compared with the non Veteran group at the same level and frequency.

DISCUSSION

Participants With a History of High Intensity Noise Exposure Showed Reduced ABR Wave I Amplitudes

These results indicate a reduction in ABR wave I amplitude in young military Veterans with high levels of lifetime noise exposure as compared with non Veteran controls and Veterans with lower levels of reported noise exposure. Wave I amplitude is reduced in animal models of noise-induced and age-related cochlear synaptopathy (Kujawa & Liberman 2009; Lin et al. 2011; Furman et al. 2013; Sergeyenko et al. 2013). Although a direct comparison of

synaptic ribbon count and ABR wave I amplitude has not yet been possible in humans, human temporal bone studies show decreases in synaptic ribbons and spiral ganglion cells with age that parallel an age-related reduction in ABR wave I amplitude (Makary et al. 2011; Konrad-Martin et al. 2012; Viana et al. 2015). This suggests that the correlation between wave I amplitude and synaptic survival may apply to humans. Our finding of a reduction in ABR wave I amplitude in young Veterans with high levels of reported noise exposure and normal pure-tone thresholds is consistent with the data from animal models of noise-induced cochlear synaptopathy. Similarly, non Veterans reporting a history of firearm use showed decreased ABR wave I amplitudes as compared with the groups with less reported noise exposure history. An evaluation of the LENS-Q scores for the non Veteran control and non Veteran Firearms groups indicated that the group differences in noise exposure were primarily based on a history of firearm use. Most previous animal studies of noise-induced cochlear synaptopathy have employed continuous noise exposure to induce synaptopathy (Kujawa & Liberman 2009; Lin et al. 2011; Furman et al. 2013). However, mice with a history of blast exposure show a reduction in synaptic ribbons in the apex of the cochlea, without loss of OHCs in that region, suggesting that impulse noise may also result in cochlear synaptopathy (Cho et al. 2013). The present study cannot confirm that the observed reductions in ABR wave I amplitude are related to synaptic loss. Decreased ABR wave I amplitudes could also indicate changes in OHC function that were not revealed by the DPOAEs, or damage to IHCs or the auditory nerve unrelated to the IHC-auditory nerve synapse. However, the possibility that the ABR results are associated with synaptopathy cannot be ruled out.

These results are consistent with the findings of Stamper and Johnson (2015a) showing wave I amplitude reductions for clicks and 4 kHz tonebursts in non Veteran participants who reported higher levels of noise exposure over the previous year. The results of the present study build on these previous findings by using a larger sample size (64 versus 30 participants), showing the effect of reduced ABR wave I amplitude across multiple frequencies, assessing lifetime noise exposure history with an in-depth questionnaire, and using a single statistical approach to account for multiple measurements in each participant, as well as DPOAE and sex differences between participants.

Veterans With Lower Levels of Noise Exposure Showed Similar ABR Wave I Amplitudes to Non Veteran Controls

One unexpected finding was that the ABR wave I amplitudes in the Veteran Low Noise group were similar to those seen in the non Veteran controls. This was surprising considering all but one of the Veterans who completed the LENS-Q reported some history of firearm use during their military service. However, the individuals in the Veteran Low Noise group most likely used firearms only during their military training, rather than in a combat situation. In this controlled environment, they may have been more likely to consistently use adequate hearing protection and to wear it correctly than participants in the Veteran High Noise or non Veteran Firearms group. This hypothesis is supported by the observation that the Veteran Low Noise group had a lower mean LENS-Q score than the non Veteran Firearms group.

Reduced ABR Wave I Amplitudes Were Not Confined to the 4 kHz Region

In contrast to animal models in which noise-induced synaptopathy was limited to the frequency range above the noise exposure band (Kujawa & Liberman 2009; Lin et al. 2011; Furman et al. 2013), our results show decreased ABR wave I amplitudes in the higher noise exposure groups at all frequencies tested (1, 3, 4, and 6 kHz). Considering the frequency region around 4 kHz is known to be particularly vulnerable to noise exposure in humans (Wilson & McArdle 2013), one might expect noise-induced ABR wave I amplitude reduction to be restricted to that region.

One possible explanation for the differing results in human and animal models is that the level and frequency content of the noise encountered during military service and recreational firearm use can be expected to be much more varied than the controlled band-limited noise exposures used in animal studies. High intensity level exposures to broadband noise, such as an impulse noise or blasts, may be more likely to cause synaptic damage throughout the cochlea than noise exposures confined to an octave band. A mouse model of blast exposure showed loss of synaptic ribbons in the apical (low frequency) and middle regions of the cochlea although the blast-related hair cell loss was confined to the base (high-frequency region, Cho et al. 2013).

Alternatively, the observation of reduced wave I amplitude across multiple frequencies seen in this study may be related to the long post exposure time. In animal models of synaptopathy, noise-exposed animals are assessed several weeks post exposure (Kujawa & Liberman 2009; Lin et al. 2011; Furman et al. 2013). In our participants, ABR assessment occurred many months to years after noise exposure. Exposure to a single episode of high intensity noise has been shown to accelerate age-related synaptopathy in mice, resulting in the spread of synaptopathy toward the apical end of the cochlea over time (Fernandez et al. 2015). Therefore, it is possible our participants may have initially experienced noise-induced synaptopathy confined to the 4 kHz region that spread with time to a broader frequency range.

The broad frequency range over which ABR wave I amplitude decreases were observed may also reflect a loss of frequency specificity for the toneburst stimuli at high intensity levels due to the spread of excitation. This may have resulted in apparent noise exposure effects on wave I amplitude at 1 kHz that were actually reflective of synaptic changes at a higher frequency.

Noise-Induced Reduction in ABR Wave I Amplitude May Be Followed by Central Hyperactivity or Disinhibition

The lack of any reduction in ABR wave III and V amplitudes in the noise exposure groups showing a reduced wave I amplitude is consistent with animal studies of synaptopathy. In mice with noise- or age-related cochlear synaptopathy, although reductions in wave I amplitude are observed in older and noise-exposed animals, there is no decrease in wave V amplitude (Sergeyenko et al. 2013; Hickox & Liberman 2014). In addition, individuals with normal pure-tone thresholds who report tinnitus show smaller wave I amplitudes, but similar or larger wave III and V amplitudes compared with their non tinnitus counterparts (Schaette

& McAlpine 2011; Gu et al. 2012). Although the participants in the tinnitus studies were not evaluated for noise exposure history, tinnitus has been proposed as a potential perceptual consequence of synaptopathy, and the pattern of ABR amplitudes observed in the individuals with tinnitus is very similar to what was observed in the present study (Schaette & McAlpine 2011; Gu et al. 2012). The absence of a change in amplitude for the later ABR waves has been interpreted as evidence of either hyperactivity or loss of inhibition in the central auditory system in response to decreased peripheral input (Schaette & McAlpine 2011; Gu et al. 2012; Hickox & Liberman 2014). Given that wave III shows no evidence of a noise- or tinnitus-related reduction in amplitude, these central changes seem to occur early in the auditory pathway.

Previously Reported Sex Differences in ABR Wave I Amplitude May Be Impacted By Differing Noise Exposure Histories

Correlations between sex and ABR wave I amplitude have been reported in the literature, with smaller wave I amplitudes for males than females even when auditory thresholds are similar (Trune et al. 1988; Mitchell et al. 1989). In the present study, we observed only weak sex differences in ABR wave I amplitude after accounting for lifetime noise exposure history. Although this study was not designed to detect sex differences in ABR wave I amplitude, these results suggest that varying noise exposure histories between male and female participants may have contributed in part to previously reported sex differences in human wave I amplitude. In our experience, finding young male non Veterans who had never used a firearm was much more difficult than identifying similar female participants. This suggests that young males may be more likely to have experienced noise levels sufficient to reduce ABR wave I amplitude than females. This may explain why Stamper and Johnson (2015b) found a reduction in ABR wave I amplitude that was associated with greater reported noise exposure history in females, but could not show the same relationship in males. In their study, participants were questioned about exposure to nine “high noise situations,” but they were not queried about firearm use. If male participants were more likely than females to have had even a single exposure to firearms in their lifetime and this was not captured by their reported noise exposure, this could explain the differing findings in males and females.

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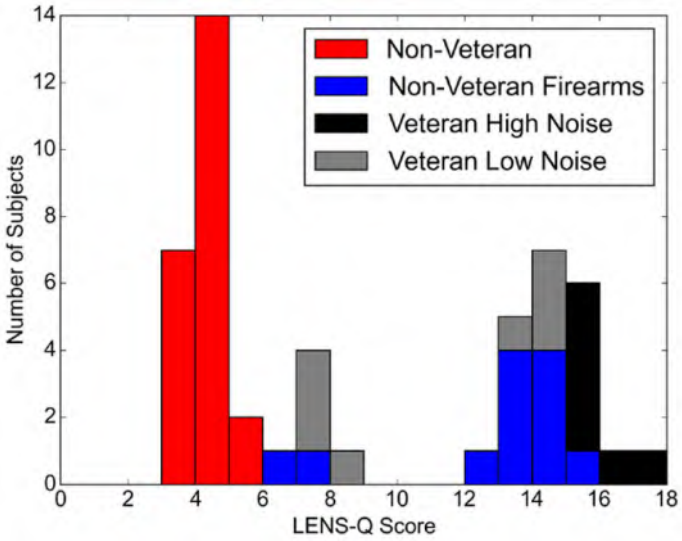

Fig. 1.

Distribution of LENS-Q scores. Distribution of the LENS-Q scores shown as a stacked barplot for 50 of the 64 study participants. The distribution is broken down by noise exposure group (final group assignments were used—see “Results” section). The remaining 14 participants were categorized into a noise exposure group based on the noise exposure interview alone. Each integer increase in LENS-Q score indicates a 10-fold increase in lifetime noise exposure. Note that the bars in this plot are stacked (e.g., 3 participants from the Veteran Low Noise group had LENS-Q scores of 7 to 8). LENS-Q indicates Lifetime Exposure of Noise and Solvents Questionnaire.

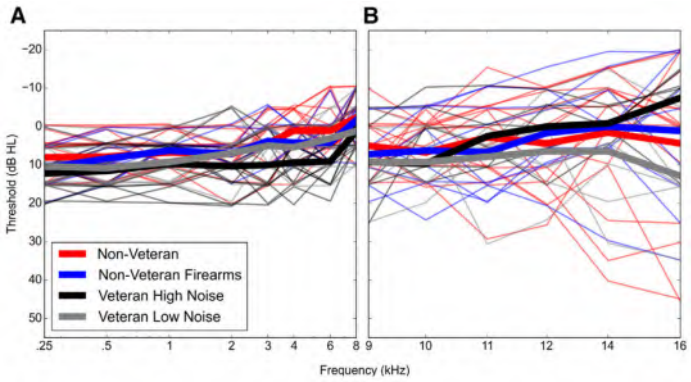

Fig. 2.

Audiometric pure-tone thresholds by noise exposure group. No systematic differences in pure-tone thresholds were observed between noise exposure groups. Audiometric pure-tone thresholds for the test ear are shown for individual study participants (thin lines), as well as the mean thresholds for each exposure group (thick lines). Color indicates the noise exposure group. Pure-tone thresholds were measured for all participants from 0.25 to 8 kHz (A) and in 38 participants from 9 to 16 kHz (B).

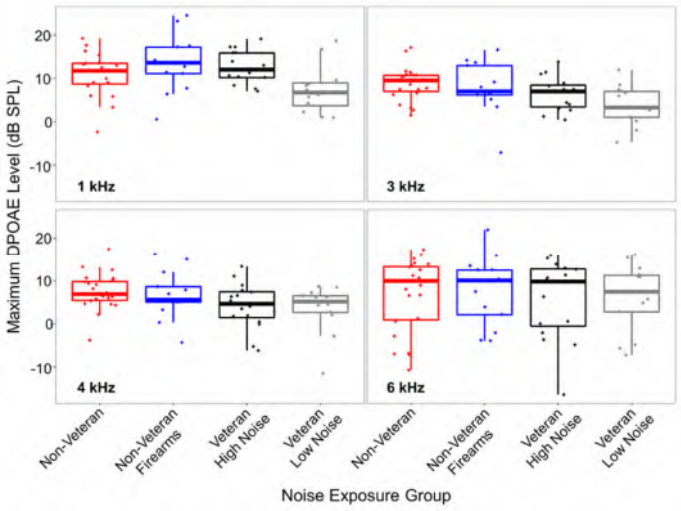

Fig. 3.

Maximum DPOAE levels across noise exposure group and frequency. DPOAE levels were similar across noise exposure groups. Maximum DPOAE levels were obtained from I/O functions at 1, 3, 4, and 6 kHz. In these boxplots, the line in the middle of the box represents the median value, the bottom and top of the box represent the 1st and 3rd quartile, respectively, and the end of the whiskers indicate the points furthest from the box that still fall within 1.5 interquartile ranges from the edge of the box. The dots indicate the maximum DPOAE level for each participant. DPOAE indicates distortion product otoacoustic emission; I/O, input/output.

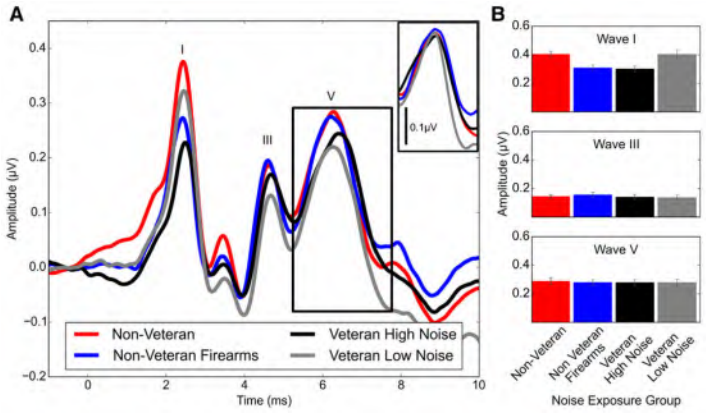

Fig. 4.

Mean ABR waveforms and peak amplitudes by noise exposure group. ABR wave I amplitude was reduced in the Veteran High Noise and non Veteran Firearms groups compared with the non Veteran control and Veteran Low Noise groups, while waves III and V were similar across groups. A, Waveforms were generated in response to a 110 dB p-pe SPL 4 kHz toneburst and averaged across all participants in each group. The peaks of waves I, III, and V are labeled. The inset shows the average wave V peak after correcting for variability in peak latency across participants. B, Wave amplitudes were measured from responses to a 110 dB p-pe SPL 4 kHz toneburst and then averaged across groups. Wave I and III amplitudes were measured as the difference in voltage between the wave peak and the following trough. Due to difficulty identifying the wave V trough in some participants, wave V amplitude was measured as the voltage difference between the wave V peak and the prestimulus baseline (average voltage measured for the 1-msec period of time before the stimulus presentation). Error bars indicate the standard error of the mean. ABR indicates auditory brainstem response.

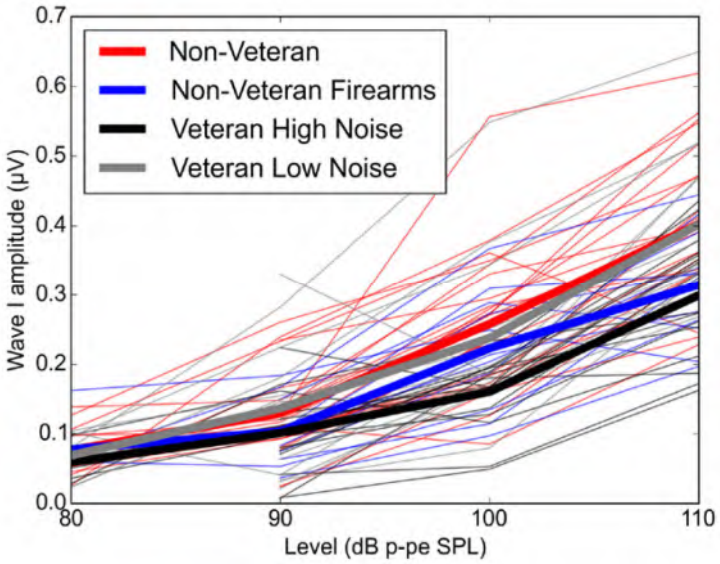

Fig. 5.

ABR input/output functions across noise exposure group. At higher stimulus levels, the Veteran High Noise and the non Veteran Firearms groups show reduced ABR wave I amplitude compared with the groups with less noise exposure history. I/O functions are shown for a 110 dB p-pe SPL 4 kHz stimulus. The thin lines represent wave I amplitudes for individual participants, color-coded by noise exposure group, while the thick lines show mean values for each group. For some participants, wave I could not be identified at 80 dB p-pe SPL, resulting in less data at that level. ABR indicates auditory brainstem response; I/O, input/output.

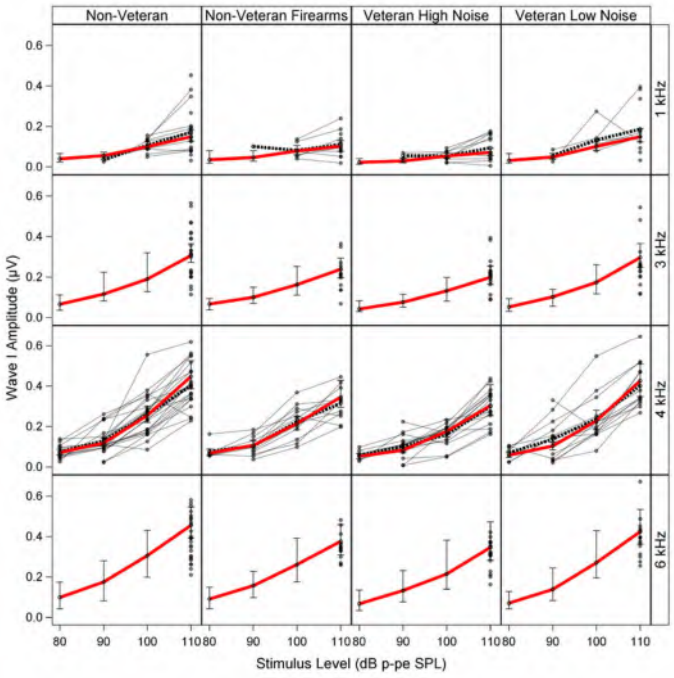

Fig. 6.

Fit of Bayesian regression model to study data. The fitted mean wave I amplitudes generated by the regression model show a good fit to the measured data across frequency and level. The fitted model is shown with a red line. The gray lines and circles indicate the measured wave I amplitudes for each participant. The black dashed line connects the sample mean wave I amplitudes at each level. The error bars are posterior 90% Bayesian confidence intervals of the fitted means. Although modeled mean wave I amplitudes are shown for all possible frequency/level combinations, no further inferences were made for frequency/level combinations where no ABR data were collected (e.g., 3 and 6 kHz for stimulus levels below 110 dB p-pe SPL). ABR indicates auditory brainstem response.

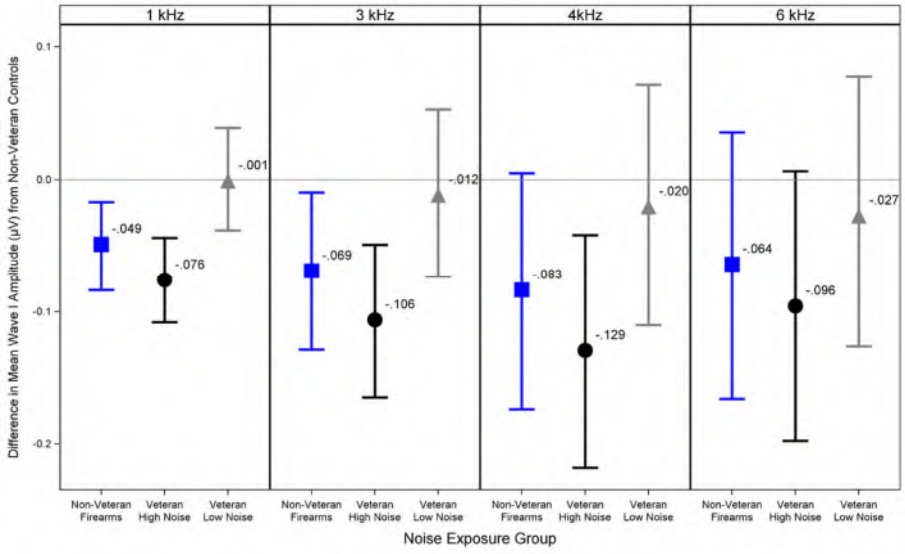

Fig. 7.

Modeled differences in group mean ABR wave I amplitudes. The Veteran High Noise and non Veteran Firearms groups show a reduction in predicted mean ABR wave I amplitude across frequency compared with the non Veteran control group. This plot shows group mean differences in ABR wave I amplitude after adjusting for sex and DPOAE levels by Bayesian regression. The difference in mean wave I amplitude for each noise exposure group compared with the non Veteran controls (in μV) is shown for a 110 dB p-pe SPL stimulus at each of the four tested frequencies. Values below the 0 line indicate a decrease in wave I amplitude compared with the non Veterans, while values above the line indicate an increase. Error bars show posterior 90% Bayesian confidence intervals. ABR indicates auditory brainstem response; DPOAE, distortion product otoacoustic emission.

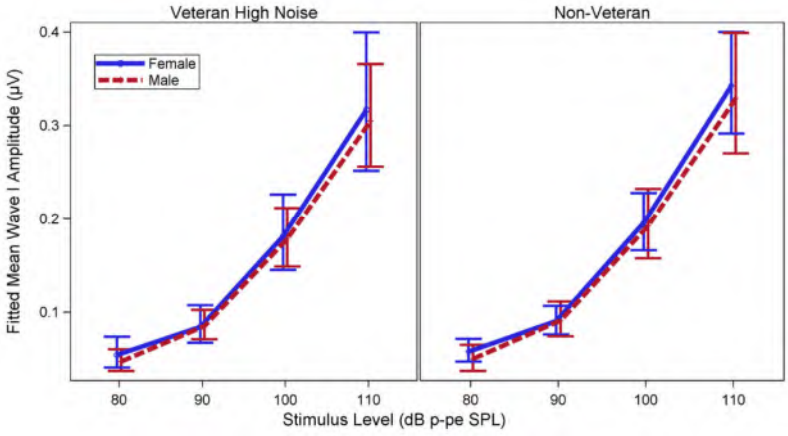

Fig. 8.

Modeled mean ABR wave I amplitude I/O functions by sex. Fitted mean ABR wave I amplitude I/O functions for the Veteran High Noise and non Veteran control groups show only weak effects of sex. I/O functions predicted by the Bayesian regression model are plotted for a 4 kHz toneburst stimulus and a DPOAE maximum level at 4 kHz of 5 dB SPL. Females are indicated by the solid blue line and males by the dashed red line. Error bars indicate posterior 90% Bayesian confidence intervals. Imbalances in the number of males vs. females for each group are reflected in the width of the confidence intervals. Plotted lines for males and females are slightly shifted horizontally to prevent overlap in the plot. Actual differences in mean wave I amplitudes are very small 0.013 μV (CI = −0.047 to 0.072) greater in females than males in the Veteran High Noise group at 110 dB p-pe SPL and 0.018 μV (CI = −0.071–0.095) greater in females in the non Veteran group). ABR indicates auditory brainstem response; CI, confidence interval; DPOAE, distortion product otoacoustic emission; I/O, input/output.

TABLE 1

Subject characteristics by noise exposure group

	Non Veteran	Non Veteran Firearms	Veteran Low Noise	Veteran High Noise
Mean age in years	25.74	25.92	30.00	26.75
Number of males	5	6	6	14
Mean PTA in dB HL (0.5, 1, and 2 kHz)	7.25	7.22	8.97	10.52
Mean high-frequency PTA in dB HL (3, 4, and 6 kHz)	2.17	4.03	4.49	9.48
Mean LENS-Q score	4.28	12.83	11.10	15.83
Total subjects	23	12	13	16

Subject characteristics are shown for each of the four noise exposure groups. The PTA is the average of the pure-tone thresholds at 0.5, 1 and 2 kHz, while the high-frequency PTA consists of the thresholds at 3, 4, and 6 kHz. The score on the LENS-Q provides a measure of lifetime noise exposure to occupational, military, and recreational noise sources.

LENS-Q, Lifetime Exposure of Noise and Solvents Questionnaire; PTA, pure-tone average.

TABLE 2

Mean fitted ABR wave I amplitude (in μV) across noise exposure group

	Non Veteran	Non Veteran Firearms	Veteran High Noise	Veteran Low Noise
1 kHz				
80 dB	0.04 (0.02–0.06)	0.03 (0.02–0.08)	0.02 (0.01–0.04)	0.03 (0.02–0.06)
90 dB	0.05 (0.04–0.07)	0.05 (0.03–0.08)	0.03 (0.02–0.05)	0.05 (0.03–0.07)
100 dB	0.10 (0.08–0.12)	0.08 (0.06–0.10)	0.05 (0.04–0.07)	0.10 (0.08–0.12)
110 dB	0.15 (0.12–0.18)	0.10 (0.08–0.13)	0.07 (0.06–0.10)	0.15 (0.12–0.18)
3 kHz				
110 dB	0.31 (0.27–0.36)	0.24 (0.20–0.29)	0.20 (0.17–0.24)	0.30 (0.25–0.35)
4 kHz				
80 dB	0.07 (0.06–0.09)	0.07 (0.05–0.09)	0.05 (0.04–0.07)	0.06 (0.05–0.07)
90 dB	0.12 (0.10–0.14)	0.11 (0.09–0.13)	0.08 (0.07–0.10)	0.10 (0.09–0.12)
100 dB	0.26 (0.22–0.30)	0.22 (0.18–0.26)	0.18 (0.15–0.22)	0.23 (0.19–0.28)
110 dB	0.44 (0.38–0.52)	0.35 (0.29–0.43)	0.31 (0.26–0.38)	0.42 (0.35–0.51)
6 kHz				
110 dB	0.45 (0.38–0.53)	0.38 (0.31–0.47)	0.35 (0.29–0.43)	0.42 (0.35–0.51)

Mean fitted ABR wave I amplitudes (in μV) are listed for each noise exposure group and stimulus frequency/level combination. Levels are in dB p-pe SPL. Posterior 90% Bayesian confidence intervals of the fitted means are shown in parentheses. These values assume maximum DPOAE levels of 5 dB SPL and are averaged over males and females. Differences in wave I amplitude can be observed between the lower noise exposure groups (non Veteran and Veteran Low Noise) and the higher noise exposure groups (non Veteran Firearms and Veteran High Noise) across frequency, with the largest differences at the highest stimulus levels.

ABR, auditory brainstem response; DPOAE, distortion product otoacoustic emission.

TABLE 3

Probability that group mean ABR wave I amplitude is lower than in the non Veteran Control group

Group	1 kHz (%)	3 kHz (%)	4 kHz (%)	6 kHz (%)
Veteran high noise	99.95	99.75	99.05	93.90
Veteran low noise	51.30	62.05	64.45	66.60
Non Veteran firearms	99.40	97.10	94.30	86.65

The probability that noise exposure group mean ABR wave I amplitude is lower than in the non Veteran control group is shown for a 110 dB p-pe SPL stimulus at each tested frequency. These probabilities are calculated from the Bayesian regression analysis. The highest probabilities are seen in the Veteran High Noise and non Veteran Firearms groups.

ABR indicates auditory brainstem response.

McMaster University | HEALTH FORUM

Rapid Evidence Profile

Examining the association between noise exposure and delayed hearing loss

10 May 2024

[MHF product code: REP 71]

Box 1: Evidence and other types of information

+ Global evidence drawn upon

Evidence syntheses selected based on relevance, quality, and recency of search

+ Forms of domestic evidence used (🍁 = Canadian)

Data analytics

Modeling

*** Additional notable features**

Prepared in three-business days using an 'all hands on deck' approach

Context

- Much of the existing literature notes that the effects of exposure to noise cease once the exposure itself has stopped.
- However, there is some concern that exposure to particular types of noise may result in hearing loss later in life despite not showing up on audiograms shortly after the exposure.

Questions

- Does significant noise exposure, without losses on audiogram at the time or shortly after the noise exposure ceases, cause an increased incidence or severity of hearing loss in the long term?

High-level summary of key findings

- We identified 12 evidence documents, of which we determined eight to be highly relevant, which include one recent low-quality evidence synthesis and seven single studies that directly address the question.
- Most of the studies examined cochlear synaptopathy – damage to the auditory nerve – as a potential explanation for the delay in measurable hearing loss using an audiogram.
- Mixed findings were reported for effects of noise exposure on cochlear synaptopathy, with one recent low-quality evidence synthesis reporting little association, while single studies examining military and Veteran personnel reported evidence of biomarkers consistent with cochlear synaptopathy from noise exposure while controlling for age.

Framework to organize what we looked for

- Population exposed to noise
  - Civilian/general population
  - Military personnel
- Type of noise exposure
  - Impulsive noise exposure
    - One-off
    - Repetitive exposure

    - Steady or continuous noise exposure
        - One-off
        - Repetitive exposure
- Level of noise exposure
    - 0–85 dBA
    - 85–110 dBA
    - 110–140 dBA
    - Over 140 dBA
- Time elapsed since noise exposure and resulting measurement for hearing loss
- Extent of hearing loss later in life
    - Mild hearing loss (26–40 dBs)
    - Moderate hearing loss (41–60 dBs)
    - Severe hearing loss (61–80 dBs)
    - Profound hearing loss (more than 81 dBs)
- Additional effects of noise exposure experienced later in life
    - Tinnitus

What we found

We identified 12 evidence documents, of which we determined eight to be highly relevant. These include:

- one recent low-quality evidence synthesis
- seven single studies.

Studies were determined to be medium or low relevancy because they did not report on a delay in the measurement of perception of hearing loss.

Coverage by and gaps in existing evidence syntheses and domestic evidence

Though there is a significant evidence base examining and categorizing hearing loss and tinnitus in the military, very little of it directly addressed the question of delayed hearing loss or delayed detection of hearing loss. An emerging hypothesis is that damage to the auditory nerve – cochlear synaptopathy – resulting from noise exposure and aging that is not detectable on audiograms after noise exposure may be the cause of the delay in hearing loss. However, the evidence available about this hypothesis is still nascent. Evidence syntheses and studies addressing cochlear synaptopathy focused on impulsive noise exposure, however no threshold level of noise exposure needed to result in cochlear synaptopathy was reported. In addition, history of noise exposure was based on self-reports rather than empirical measurements.

We did not include animal studies as part of this profile, but we have identified potentially relevant animal studies in Appendix 4.

Box 2: Approach and supporting materials

We identified evidence addressing the question by searching Health Systems Evidence, ACCESSSS, PubMed, and CINAHL. All searches were conducted on 29 April 2024. The search strategies used are included in Appendix 1. In contrast to synthesis methods that provide an in-depth understanding of the evidence, this profile focuses on providing an overview and key insights from relevant documents.

We searched for full evidence syntheses (or synthesis-derived products such as overviews of evidence syntheses), protocols for evidence syntheses, and single studies.

We appraised the methodological quality of evidence syntheses that were deemed to be highly relevant using the first version of the AMSTAR tool. AMSTAR rates overall quality on a scale of 0 to 11, where 11/11 represents a review of the highest quality, medium-quality evidence syntheses are those with scores between four and seven, and low-quality evidence syntheses are those with scores less than four. The AMSTAR tool was developed to assess reviews focused on clinical interventions, so not all criteria apply to evidence syntheses pertaining to delivery, financial or governance arrangements within health systems or implementation strategies.

A separate appendix document includes:

1) methodological details (Appendix 1)
2) details about each included evidence synthesis (Appendix 2)
3) details about each included single study (Appendix 3)
4) excluded evidence documents that were based on animal studies (Appendix 4)
5) documents that were excluded in the final stages of review (Appendix 5).

This rapid evidence profile was prepared in the equivalent of three days of a ‘full court press’ by all involved staff.

Key findings from included evidence documents

Most of the identified evidence documents – the recent low-quality evidence synthesis and five of the singles studies – report on 'hidden hearing loss' despite normal audiograms.(1) These studies point to cochlear synaptopathy, which describes the loss of synapses that connect inner hair cells to the auditory nerve and can produce below-threshold levels of abnormalities including speech-in-noise difficulties and tinnitus that overtime can progress to more substantial hearing loss. The auditory nerve is more vulnerable than other parts of the cochlear structure to aging and to noise exposure; however, damage to the nerve tends to disrupt encoding of complex information, such as speech, rather than single tones and so may not be detected as part of typical audiograms.

While cochlear synaptopathy is well established in animals, its occurrence in humans is less well understood as well-established approaches to its detection are invasive and involve examining the temporal bone post-mortem. More recently, studies have begun using biomarkers to better understand the occurrence of cochlear synaptopathy among individuals and its association with noise exposure and aging.

The evidence documents we identified revealed mixed effects for the association between noise exposure and aging on cochlear synaptopathy. The recent low-quality evidence synthesis, which included a meta-analysis, found conclusive evidence of the relationship between reduced auditory nerve function and age, but identified only a weak association between noise exposure history and auditory nerve responses.(1) In contrast, all five single studies report biomarkers consistent with cochlear synaptopathy among military personnel and Veterans with a history of impulsive noise exposure.(2-6)

We also identified two studies related to new-onset and progressive hearing loss among U.S. military members and Veterans more generally. One study re-analyzed data from three published studies on the effects of noise exposure on the progression of hearing loss and found that noise exposure can accelerate the progression of hearing loss where the hearing loss is absent or mild at the end of military service (i.e., threshold levels up to 50 db HL).(7)

The final study found that in a significant sample of U.S. military members (n=48,000), 7.5% reported new-onset hearing loss during follow-up surveys administered three years after the baseline reporting. New-onset hearing loss was associated with a history of combat deployment, being male, and older age. Among deployed military members, new-onset hearing loss was associated with reported proximity to improvised explosive devices and having experienced a combat-related head injury.(8)

Next steps based on the identified evidence

Though the evidence-base for this question is still evolving, there are existing efforts to address gaps in evidence about military service and auditory disorders. In particular, the Institute of Medicine in the U.S. issued a recommendation for a large-scale longitudinal cohort study to examine the long-term effects of noise exposure during military careers. This work was taken up by investigators at the Veterans Affairs Rehabilitation Research and Development National Center for Rehabilitative Auditory Research in Portland, who are now running a longitudinal cohort study with Veterans, which could be an important source of future data to help answer this question.

Waddell K, Wu N, Demaio P, Bain T, Bhuiya A, Wilson MG. Rapid evidence profile #71: Examining the association between noise exposure and hearing loss. Hamilton: McMaster Health Forum, 10 May 2024.

This rapid evidence profile was funded by the Chronic Pain Centre of Excellence for Canadian Veterans and the Atlas Institute for Veterans and Families, which in turn are funded by Veterans Affairs Canada. The McMaster Health Forum receives both financial and in-kind support from McMaster University. The views expressed in the rapid evidence profile are the views of the authors and should not be taken to represent the views of the Chronic Pain Centre of Excellence for Canadian Veterans, the Atlas Institute for Veterans and Families or McMaster University.

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Table 1A – EXTENDED – per CCOHS **Noise Exposure Limits when Criterion Level = 85 dBA**		
3 dBA Exchange Rate Allowable Level dBA	Maximum Permitted Daily Duration (hours)	5 dBA Exchange Rate Allowable Level dBA
85	8	85
88	4	90
91	2	95
94	1	100
97	0.5 (30 mins)	105
100	0.25 (15 mins)	110
103	7.5 minutes	115
106	3.75 minutes	120
109	1.87 minutes	125
112	56 seconds	130
115	28 seconds	135
118	14 seconds	140
121	7 seconds	145
124	3.5 seconds	150
127	1.75 seconds	155
130	0.87 seconds	160

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Noise

Noise - Occupational Exposure Limits in Canada

On this page

What are the occupational exposure limits for workplace noise?

Occupational exposure limits (OELs) for noise are typically given as the maximum duration of exposure permitted for various noise levels. They are often displayed in exposure-duration tables like Table 1A and Table 1B. The OELs depend on two key factors that are used to prepare exposure-duration tables: the criterion level and the exchange rate.

Table 1A
Noise Exposure Limits when Criterion Level = 85 dBA

3 dBA Exchange Rate	Maximum Permitted Daily Duration (hours)	5 dBA Exchange Rate
Allowable Level dBA		Allowable Level dBA
85	8	85
88	4	90
91	2	95
94	1	100
97	0.5	105
100	0.25	110

Table 1B Noise Exposure Limits when Criterion Level = 90 dBA		
3 dBA Exchange Rate	Maximum Permitted Daily Duration (hours)	5 dBA Exchange Rate
Allowable Level dBA		Allowable Level dBA
90	8	90
93	4	95
96	2	100
99	1	105
102	0.5	110
105	0.25	115

What is the criterion level?

The criterion level, often abbreviated as Lc, is the steady noise level permitted for a full eight-hour work shift. This criterion level is 85 dBA in most jurisdictions, but it is 87 dBA for organizations that follow the Canadian federal noise regulations.

What is the exchange rate?

As the sound level increases above the criterion level, Lc, the allowed exposure time must be decreased. The allowed maximum exposure time is calculated by using an exchange rate, also called a "dose-trading relation" or "trading ratio." The exchange rate is the amount by which the permitted sound level may increase if the exposure time is halved.

There are two types of exchange rates currently in use: 3 dBA exchange rate or the "3 dB rule," and 5 dBA exchange rate or the "5 dB rule." These two exchange rates, with criterion levels of 85 dBA and 90 dBA, give two different sets of exposure guidelines, as Table 1A and 1B show.

The 3 dBA exchange rate is more stringent. For example, the maximum permitted duration for a 100 dBA noise exposure in the 3 dBA exchange rate is 15 minutes. With the 5 dBA exchange rate, it is one hour.

Most experts recognize the 3 dB rule as more logical. They argue that it is logical that if the sound level is doubled, then the allowable exposure time should be cut in half. It follows, then, that the allowable time should be halved for every 3 dBA increase in sound level. This is precisely the case if the 3 dBA exchange rate is used.

The table below shows the criterion levels (i.e., maximum permitted exposure levels for 8 hours) and the exchange rates used in different Canadian jurisdictions.

What are the noise exposure limits in Canadian jurisdictions?

Jurisdiction (federal, provincial, territorial)	Continuous Noise*[1]		Impulse / Impact Noise[1 and *]	
	Maximum Permitted Exposure Level for 8 Hours: dB(A)	Exchange Rate dB(A)[2] +	Maximum Peak Pressure Level dB(peak)	Maximum Number of Impacts
Canada (Federal)	87	3	-	-
British Columbia	85	3	140	-
Alberta	85	3	-	-
Saskatchewan[4]	85	3	-	-
Manitoba	85	3	-	-
Ontario[5]	85	3	-	-
Quebec	85	3	140	-
New Brunswick	85	3	140	-
Nova Scotia[3]	85	3	140	-
Prince Edward Island	85	3	-	-
Newfoundland and Labrador[3]	85	3	140	-
Northwest Territories[4 and *]	85	-	140	100
Nunavut[4 and *]	85	-	140	-

Yukon Territories	85	3	140	90

1. For more information about continuous, impulse and impact noise, please see Noise - Basic Information.

2. When a 3 dB exchange rate is used, generally, there is no separate regulation for impulse/impact noise. The equivalent sound exposure level (L_{ex}) takes impulse noise into account in the same way as it does that for continuous or intermittent noise. Noise regulations in several jurisdictions treat impulse noise separately from continuous noise. A common approach is to limit the number of impulses at a given peak pressure over a workday. The exact figures vary slightly, but generally the regulations in which the exchange rate is 5 dB permit 10,000 impulses at a peak pressure level of 120 dB; 1,000 impulses at 130 dB; 100 impulses at 140 dB, and none above 140 dB.

3. The regulations in these jurisdictions do not specify a value but reference the ACGIH TLVs.

4. The regulations in these jurisdictions indicate that over an exposure limit of 85 dBA Lex or an “at any time” sound level limit of 90 dBA, the employer is required to provide hearing protection, train workers, and implement audiometric testing. dBA Lex means the level of a worker's total exposure to noise in dBA is averaged over an entire workday and adjusted to an equivalent eight-hour exposure. These jurisdictions also do not allow unprotected exposures for sound levels that exceed 90 dBA. Even when the equivalent exposure is less than 85 dBA, if a worker is exposed at any time at sound levels equal to or above 90 dBA, the employer is required to take the protective measures.

5. The Ontario Noise regulation requires that the employer must make sure that no worker is exposed to a sound level greater than a time-weighted average exposure limit of 85 dBA measured over an 8-hour work day. Employers must follow the “hierarchy of controls”, which uses engineering controls and work practices to protect workers and places restrictions on the use of hearing protection devices (HPDs) by workers.

* In both territories, the Mine Health and Safety Regulations reference the 3 dBA exchange rate and the maximum impulse level of 140 dB. Please contact Northwest Territories or Nunavut for further information.

Where do you find noise exposure limits in Canadian legislation?

The following are references to the federal, provincial, and territorial legislation where you will find the occupational noise exposure limits from the different jurisdictions in Canada. Since legislation is amended from time to time, the jurisdiction should be contacted for the most current information about the noise exposure limits and how they are enforced. This information is intended as a guide only and may not apply to specific occupational sectors (for example, mining). The regulations should also be consulted for information on requirements for hearing protective equipment and other control measures that may be prescribed for protecting the hearing of workers. Please contact your local office of the occupational health and safety agency for your jurisdiction if you have specific questions that apply to your workplace.

Canada (Federal)

Canada Labour Code, Part II, (R.S.C. 1985, c. L-2)
Canada Occupational Safety and Health Regulations, (SOR/86-304)
Section 7.4(1)(b)

British Columbia

Worker's Compensation Act
Occupational Health and Safety Regulations (BC Reg 296/97 as amended)
Section 7.2 [B.C. Reg. 382/2004, s.1]

Alberta

Occupational Health and Safety Code, 2023
Part 16

Saskatchewan

Saskatchewan Employment Act, S-15.1
Occupational Health and Safety Regulations, 2020
PART 8 Noise Control and Hearing Conservation

Manitoba

Workplace Safety and Health Act [R.S.M. 1987, c. W210]
Workplace Safety and Health Regulation (Man. Reg. 217/2006) Part 12

Ontario

Occupational Health and Safety Act [R.S.O. 1990, c.1]
Noise (O. Reg. 381/15)

Quebec

Act Respecting Occupational Health and Safety [R.S.Q., c.2.1]
Regulation respecting Occupational Health and Safety (O.C.885-2001)
Division XV, Sections 130-141.5

New Brunswick

Occupational Health and Safety Act
General Regulation (N.B reg. 91-191 as amended)
Part V, Sections 29 to 33

Nova Scotia

Workplace Health and Safety Regulations
N.S. Reg. 52/2013
Part 2, Section 2.1 to 2.3
(references ACGIH TLVs® physical agents, as updated annually)

Prince Edward Island

Occupational Health and Safety Act
Occupational Health and Safety Act General Regulations (E.C. 180/87)
Part 8, Section 8.3

Newfoundland and Labrador

Occupational Health and Safety Act
Occupational Health and Safety Regulations, 2012
Section 68
(references ACGIH TLVs®, as updated annually)

Northwest Territories

Safety Act
Occupational Health and Safety Regulations, R-039-2015
Part 8 Noise Control And Hearing Conservation

Nunavut

Safety Act
Occupational Health and Safety Regulations, R-003-2016
Part 8 Noise Control and Hearing Conservation

Yukon Territories

Occupational Health and Safety Act
Occupational Health Regulations (O.I.C. 1986/164)
Section 4

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Prelude: Noise-induced tinnitus and hearing loss in the military

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ABSTRACT

Hearing is critical to the performance of military personnel and is integral to the rapid and accurate processing of speech information. Thus, noise-induced hearing loss (NIHL) represents a severe impairment that reduces military effectiveness, safety, and quality of life. With the high levels of noise to which military personnel are exposed and the limited protection afforded by hearing conservation programs, it should be no surprise that annual Veterans Affairs disability payments for tinnitus and hearing loss exceeded $1.2 billion for 2009 and continue to increase. Military personnel work in high-noise environments, yet the Department of Defense (DoD) cannot predict who is susceptible to noise-induced hearing loss and tinnitus. Of those exposed to noise, 80% may also suffer from chronic tinnitus. Despite its prevalence, there are no means to objectively measure the severity of tinnitus in those individuals. A fundamental understanding of the underlying mechanisms of tinnitus and its relation to noise-induced hearing loss is critical. Such an understanding may provide insight to who is at risk for each condition, allow aggressive hearing protection measures in those individuals most at risk, and create areas for treatment for those already suffering from the conditions. The current review will address the scope of the problems of NIHL and tinnitus for the military, discuss the noise environments in which military personnel operate, describe the hearing conservation measures currently in place, and the challenges those programs face. Some recent breakthroughs in NIHL research will be discussed along with some challenges and directions for future research on NIHL and tinnitus.

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1. Financial and personal cost of hearing loss and tinnitus

Hearing loss and tinnitus are significant public health issues in the United States and worldwide. The prevalence of these conditions amongst military personnel is considerably greater than in the general public. In the U.S. Department of Veterans Affairs (VA), the number one and number two disability compensations for veterans are tinnitus and hearing loss (VA, 2011). The U.S. Government Accountability Office (GAO) report on noise (2011) indicates that hearing loss is the most prevalent occupational health disability in the Department of Defense (DoD). In addition, the DoD civilian worker compensation costs were approximately $56 million in FY2003 (Geiger, 2008). VA compensation costs were approximately $1.102 billion in fiscal year 2005 (FY2005) with costs for hearing loss as a primary disability. VA reports show a continued growth in cases of noise-induced hearing loss (NIHL) and tinnitus amongst military personnel. Tinnitus was the most prevalent service-connected disability for veterans receiving compensation at the end of FY2010 (744,871 cases or 23% of the total cases; 717,463 male, 27,408 female). Hearing loss was the second most prevalent disability (672,410 cases or 21% of all cases; 632,627 male, 9710 female) out of 3,210,261 veterans receiving service-connected disability benefits. In FY2010, there were 92,260 new veterans who received compensation for tinnitus (10.7% of total new cases) and 63,583 who received compensation for hearing loss (7.3% of total new cases). The growth in disability benefits for tinnitus and hearing disability represents a major challenge to the VA.

Almost every Soldier, Sailor, Airman, and Marine will be exposed to hazardous levels of noise at some point in his or her military career; many military personnel will have multiple exposures that could lead to NIHL and/or tinnitus. The 2005 Institute of Medicine study included a review of 1983–2003 data in the Defense Occupational Environmental Health Readiness System-Hearing Conservation (DOEHRS-HC) database, finding that 18% of military personnel in the database showed significant threshold shifts or other hearing degradation (Humes et al., 2005). A careful analysis of health care records shows a strong correlation between NIHL and tinnitus (Mazurek et al., 2010; Stephenson and Stephenson, 2000) (Fig. 1). The Stephenson and Stephenson (a National Institute of Occupational Safety and Health or NIOSH presentation) chart shown in Fig. 1 was based on a study of U.S. construction industry carpenters, showing the relationship of tinnitus and hearing loss in

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Acronyms

CVN	aircraft carrier, nuclear
CVX	aircraft carrier, experimental
dB(A)	decibel, A-weighted
DoD	Department of Defense
DOEHRS-HC	Defense Occupational Environmental Health Readiness System-Hearing Conservation
EFV	Expeditionary Fighting Vehicle
FY	Fiscal Year
GAO	Government Accountability Office
HP	Hearing Protection
HPD	Hearing Protection Device
IED	Improvised Explosive Device
JSF	Joint Strike Fighter
NCRAR	National Center for Rehabilitative Auditory Research
NIH	National Institutes of Health
NIHL	Noise-Induced Hearing Loss
NIOSH	National Institute for Occupational Safety and Health
ONR	Office of Naval Research
OSHA	Occupational Safety and Health Administration
PATM	Progressive Audiologic Tinnitus Management
PPE	Personal Protective Equipment
R&D	Research and Development
SBIR	Small Business Innovation Research
TBI	Traumatic Brain Injury
U.S.	United States
USA	United States of America
USMC	United States Marine Corps
VA U.S.	Department of Veterans Affairs

that population (2000). The Mazurek et al. study (2010) shows similar relationships between NIHL and chronic tinnitus. Thus, NIHL research programs should also investigate the causes of, susceptibilities to, and treatments for, tinnitus.

NIHL obtained from the workplace (occupational hearing loss) has been an important issue in the military for as long as firearms, artillery, and mechanized equipment have been employed. Impulse, impact or steady state and blast wave exposures may, depending on the level, spectrum and exposure duration, lead to either temporary or permanent threshold shift in hearing as result of damage to the sensory cells, neurons or supporting cells in the cochlea (Axelsson and Hamernik, 1987; Hamernik et al., 1984; Helfer et al., 2010; Patterson et al., 1986; and Phillips and Zajtchuk, 1989). Blast-induced tinnitus and blast-induced hearing loss are particularly important causes of disability in war veterans because these injuries are generally directly attributable to improvised explosive device (IED) or rocket propelled grenade attacks, are increasing in incidence and prevalence in U.S. military active duty and veteran populations, and are not injuries commonly found in the U.S. occupational setting (Hoffer and Balaban, 2011). Moreover, hearing loss is a common co-morbidity with traumatic brain injury (TBI), with 33% of TBI veterans showing acute, 43% sub-acute, and 9% chronic hearing loss (Hoffer and Balaban, 2011). Over 90% of veterans in one study that had blast-induced TBI reported "non-concerning" ringing/tinnitus immediately after a blast event, 70% reported tinnitus still present during the first seven days, while nearly 33% reported tinnitus present 10 days to several months after the event. These veterans also reported tinnitus at a higher rate (over 60%) after several months had passed since the blast event (Hoffer and Balaban, 2011).

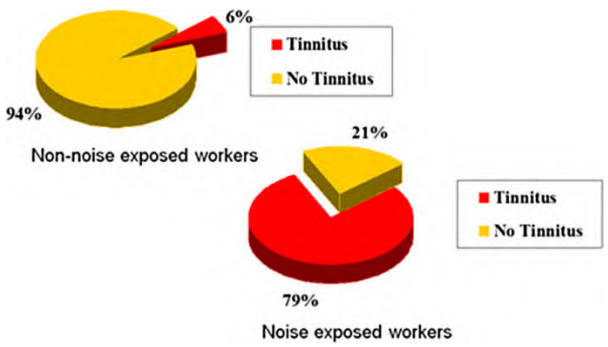

Fig. 1. Percentage of individuals with tinnitus or no-tinnitus in non-noise exposed workers and noise-exposed workers (From (Stephenson and Stephenson, 2000) with permission of authors; based on results of a U.S. construction industry study of NIHL and tinnitus among carpenters.).

The possible relationships and treatments for TBI, tinnitus, hearing loss, and post-traumatic stress disorder are very important and a great deal of research is being done, including strategies for treating polytrauma and multi-sensory impairment. Each factor can greatly decrease quality of life for the patient and the juxtaposition of multiple factors, causes, and relationships (including central auditory processing disorders) can increase the difficulty of treatment (Hoffer and Balaban, 2011).

Beyond the military, NIHL has been one of the most prevalent occupational health concerns in the United States over the last 25 years as reported by the U.S. Bureau of Labor Statistics (OSHA, 2011a). In the general population, approximately 30 million U.S. workers are exposed to hazardous noise levels and an additional nine million are exposed to ototoxic chemicals, resulting in 125,000 significant cases of hearing loss between 2004 and 2010, and 21,000 cases in 2009 alone (OSHA, 2011a). The U.S. Occupational Safety and Health Administration (OSHA) tracks and requires reporting of hearing loss (OSHA 29 CFR 1910.95), but does not require specific reporting of tinnitus, probably due to the subjective nature and lack of objective measures of tinnitus (OSHA, 2011b). OSHA medical surveillance requirements do discuss tracking tinnitus and hearing deficits by the occupational health provider (OSHA, 2011c; e.g., for workers exposed to inorganic lead, 29 CFR 1910.1025 Subpart Z, Appendix C III), however, better measurement tools and techniques are needed for tracking these conditions.

National Institutes of Health (NIH) researchers estimated that 22.7 million adult Americans stated they were affected by tinnitus for more than 3 months during 2009 (NIH, 2012). According to some studies, approximately 80% of personnel who show NIHL may also have tinnitus (Stephenson and Stephenson, 2000; Mazurek et al., 2010). Interestingly, the most recent VA disability compensation numbers for fiscal year 2010 show an increased incidence of tinnitus over NIHL (VA, 2011). Whereas NIHL may be measured objectively via audiograms, tinnitus is self-reported making it difficult to assess and quantify. Perceptual attributes (e.g., pitch, loudness and masking of tinnitus) may be discerned during psychoacoustic testing (Humes et al., 2005); however, these types of measures are not routinely collected or required. Instead, recurrent tinnitus is compensated as a VA disability based on self-reported subjective complaints (Beck, 2011; Fausti et al., 2009).

2. Impact of tinnitus and NIHL on performance

Military personnel depend heavily on verbal and non-verbal communication in combat operations, industrial settings, and during training scenarios. Not surprisingly, hearing acuity is a critical component of combat effectiveness. Hearing is a primary sense

the warfighter uses to detect and identify friends, foes, and non-hostile individuals, and it also plays a vital role in avoiding enemy fire and detection. The ability to hear the surrounding environment, including auditory cues, warnings, and signals, is a key part of situational awareness, survival in tactical and non-tactical situations, and accomplishing the mission. Hearing the phantom sound of tinnitus (e.g., buzzing, ringing, humming) while conducting a stealth operation represents a serious problem because it produces distracting, irrelevant and confusing auditory cues that compete with the real world acoustic cues relevant to the mission (Hallam et al., 2004; Rossiter et al., 2006). Serious or debilitating tinnitus could lead to sleep disturbances and depression, factors that would negatively impact operational readiness (Alster et al., 1993; Dobie et al., 1992; Sullivan et al., 1992). Likewise, the inability to hear important acoustic cues or communication signals emanating from the enemy or other members of one's own combat team would pose serious risks that could compromise the mission and undermine operational readiness. It is well documented that NIHL degrades combat performance through impairment of speech perception ability, especially in conditions of significant competing background noise (Blue-Terry and Letowski, 2011; Geiger, 2008; Norin et al., 2011; Ribera et al., 2004). Because military exercises and combat commonly occur in acoustic environments with high levels of background noise, impaired auditory perception due to NIHL can dramatically affect performance of military personnel (Nakashima et al., 2007; Van Wijngaarden and Rots, 2001). A number of studies have examined the performance of military personnel (e.g., tank gunner) as a function of their noise environment and the impact on hearing and communications (Garinther and Peters, 1990; Lazar et al., 1995; Price et al., 1989; Versfeld and Vos, 1997). High ambient noise environments significantly degraded communication and had serious negative consequences on performance. The negative effects of high levels of background noise are compounded by NIHL and tinnitus which pose tactical risks for individual survival and unit combat effectiveness. High-frequency hearing loss can be especially problematic for understanding speech, as well as recognizing the acoustic signatures of different weapons and military vehicles (Abel et al., 1982; Folmer et al., 1999; Skinner, 1980; Vignuelle, 2011). In addition, tinnitus is often strongly linked to other co-morbidities such as depression, anxiety, sleep deprivation and inability to concentrate (Alster et al., 1993; Folmer et al., 1999; Halford and Anderson, 1991; Hallam et al., 2004; Langguth et al., 2007).

Not only does hearing loss impair performance of military personnel, but the very devices used for hearing protection may also compromise hearing acuity. There is a fine line between successfully protecting hearing and also allowing individuals to effectively communicate and perform their duties. Casali and others have noted issues related to conventional HPDs (i.e., passive or level-independent devices that do increase attenuation as noise levels increase, allowing better speech perception, for example, as can be found in some active noise canceling HPDs). These issues include: "compromised auditory perception, degraded signal detection, reduced speech communication abilities, and diminished situational awareness" (Casali et al., 2009). Current research has not only focused on determining the effects of NIHL and tinnitus on performance of military personnel, but has also begun to investigate the effects of devices intended to provide both protection and audibility on operational performance (Casali et al., 2009). Given the magnitude of the problem, much more research is needed to investigate effects of NIHL and tinnitus on military performance and greater effort must be made to develop more sophisticated personal hearing protection devices that not only reduce the risks of developing NIHL and tinnitus, but also lead to better communication and performance in noisy combat environments.

3. Hazardous noise environments in military settings

To appreciate the problems of NIHL and tinnitus in the military requires an understanding of the extremely harsh and daunting acoustic environments in which military personnel typically work. In the civilian sector, industrial noise levels can be high, but if this occurs, workers can be rotated out of the noise to limit exposure duration. In contrast, noise levels in military operations can be significantly higher and warfighters are often required to remain in these noisy environments to complete the mission. The unique acoustic environments in the military are highlighted by comparing noise levels on a Navy aircraft carrier flight deck to land-based commercial and military airfields. For a land-based operation, the length of the runway can vary from 6000 to 11,000 feet with the flight line where personnel work located far away from the runway. Civilian airport maintenance and support personnel are located far away from the run-up and take-off areas. In most cases, flight line personnel are subjected to only engine startup and taxi noise. Airport towers direct aircraft movement from afar. In contrast, on a naval aircraft carrier, the airfield is condensed to a length of roughly 1000 feet and width of 250 feet. Aircraft and flight deck personnel are often separated by only a few inches or feet. All aircraft operations are confined to the surface area of the ship's deck. Below the flight deck in the interior of the ship is a facility that houses nearly 6000 people. Naval architects and acoustical engineers face a formidable challenge balancing the operational needs of a modern aircraft carrier while preventing military personnel from being exposed to excessive noise. It is total systems engineering which enables the integration of ship design, aircraft design, hearing conservation, and habitability standards. Yet, even with the availability of cutting-edge technology and world-class engineering, effective hearing conservation remains a major challenge due to the extremely high levels of noise generated by ship engines and other equipment (e.g., jet engines, catapults) that are capable of inducing acoustic trauma. Compounding the problem is the competing need for applying hearing conservation while maintaining the ability of naval personnel to adequately and safely communicate with one another. Off the carrier flight deck, the Sailors must have access to quiet areas within the ship. Quiet areas allow the noise-exposed auditory system to recover thereby minimizing the development of NIHL (NIOSH, 1998).

Total systems engineering is key to reducing noise in modern ship design, including flight operations aboard aircraft carriers. Aircraft flight operation noise has received considerable attention in the civilian and commercial worlds (Brink et al., 2008; Ising et al., 1990; Lin et al., 2008; Pepper et al., 2003; Van Gerven et al., 2009). From the early days of the Nimitz (CVN 68) Class, some of the largest aircraft carriers in the world, there has been documented concern for the shipboard noise levels to which the crew is exposed (Rovig et al., 2004). In light of the development of new Navy ships such as the CVX and CVN 77 and aircraft under the Joint Strike Fighter (JSF) Program, it is time to re-examine the 30-year-old CVN 68 design regulations and apply the more up to date acoustic technologies and techniques developed under the Surface Ship Silencing R&D, Submarine Silencing and Small Business Innovation Research (SBIR) Programs. These new ship design principles (including different hull shapes to reduce turbulence and increase speed; use of innovative shock, vibration, and noise dampening materials and insulation; and the increasing use of modern electronics and similar advances in material science that often equate to greatly reduced noise and vibration) would lead to greatly improved hearing conservation. With modern design principles and attention to detail, it may be possible to lower below deck noise in living areas by as much as 20 dB thereby reducing the prevalence of NIHL and tinnitus in personnel serving on aircraft carriers.

4. Prevention

Noise exposure may be controlled through isolation (distance and physical barriers), vibration dampening, insulation, and related means including proper maintenance (Humes et al., 2005). Engineering controls like these are the preferred method for prevention of damage to hearing that results in NIHL and noise-induced tinnitus. Hearing protection devices (HPDs) such as foam ear plugs, molded inserts, and sound attenuating circumaural earmuffs are limited in that they may not fully protect the person against the types and levels of noise found in the battlefield and flight deck and also may diminish speech intelligibility while they are being used. The greatest detractor to any personal protective device is the very high reliance that must be placed on individual compliance. If the individual does not remember to, or want to, wear the protection or use it correctly, he or she is not going to derive the necessary noise attenuation benefit.

Hearing conservation within military settings is a complex subject. Unlike workers in typical industrial settings who are exposed to noise for 8 h a day during a five day work week, who presumably go home to a quite environment allowing for auditory rest and recovery and limited noise dose, Sailors and Marines aboard ships and in deployed settings may have hazardous noise exposures not only in their work environment (e.g., flight deck) but also in their crew berthing areas (e.g., directly under a carrier's flight deck with noise levels potentially above 94 dB(A)). The Navy considers 85 dB(A) to be the threshold for single hearing protection (i.e., ear plugs) and 104 dB(A) for double hearing protection (i.e., ear plugs and circumaural earmuffs) for steady state noise (U.S. Navy, 2005). Noise levels on the flight deck during flight evolutions and some aircraft maintenance operations are intense and easily exceed the 104 dB(A) threshold for double hearing protection. On the gallery deck (03-level) on an aircraft carrier (i.e., just below the flight deck), noise levels regularly exceed 85 dB(A) in most spaces during flight operations. Other areas on the ship may also have hazardous levels of noise produced from installed equipment and related operations (e.g., ship propulsion and engineering spaces, industrial areas, etc.). Fig. 2 shows routine noise levels found on aircraft carriers in comparison to typical home lawnmower use, including such routine operations as movement of the jet blast deflector (a water-cooled ramp that is raised at an angle behind the launching aircraft to reduce jet engine exhaust heat and turbulence effects on aircraft lining up behind the catapult launcher).

Despite engineering advances that have reduced noise levels produced by naval ships, aircraft, and other weapons and equipment, the Navy by and large is still designing and producing equipment that has great potential to harm the hearing of Sailors and Marines in locations such as carrier decks, aircraft cockpits, expeditionary fighting vehicles, and engine rooms. Fig. 3 shows the sound levels in four high-noise work areas compared to the Navy's noise exposure standards for single and double hearing protection. The sound levels in all of these work areas routinely exceed the requirements for double hearing protection during operations (i.e., above 104 dB(A)) and often exceed the capability of available HPDs. Perfectly fitting HPDs may provide up to 30 dB(A) reduction in noise in the lab but often only achieve half or less than that in the field due to failure to maintain or wear the HPD properly (Berger and Kieper, 2000).

In spite of significant challenges in the implementation of effective hearing conservation programs for military personnel, there are many silencing technologies that can be used to reduce noise in military, industrial, recreational and home settings, similar to those already used in "quiet" household garbage disposals, dishwashers, garage door openers and refrigerators. The U.S. Navy's 30-year investment in Surface Ship and Submarine Silencing Programs has resulted in the incremental silencing of each succeeding class of ships. In terms of HPDs, the Navy's flight deck cranial helmet currently under development is predicted to reduce noise exposure by approximately 50 dB(A).

5. Naval Research

In the Office of Naval Research (ONR), the NIHL portfolio includes four major research areas (lanes) aimed at reducing and preventing noise-induced tinnitus and hearing loss. (1) Source noise reduction of ships, aircraft and other equipment. (2) Improved personal protective equipment (PPE), HPDs, in-ear dosimetry, underwater communications and hearing protection. (3) Medical treatment of tinnitus and hearing loss including cell regeneration, pharmacological interventions, blast interventions and improved pulmonary and nasal drug delivery. (4) Evaluation and assessment of hearing loss and tinnitus incidence, susceptibility and risk factors. The NIHL portfolio is nominally 19% noise control, 12% improved PPE, 43% medical research, and 26% in evaluation and assessment. This balance within lanes is anticipated to be maintained over the next few years under existing Federal budgets.

In the short term, the most effective method for reducing the risk of NIHL and tinnitus is through conscientious use of the

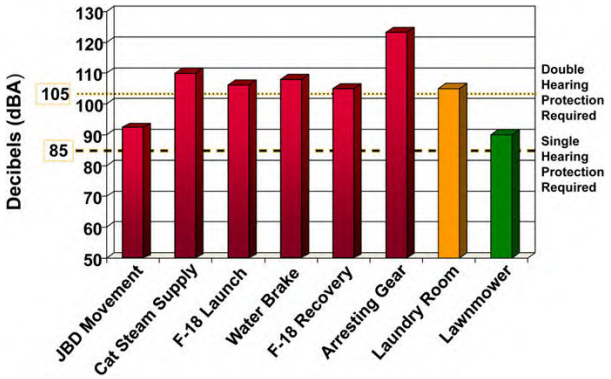

Fig. 2. Noise levels expressed in dB(A) generated by various naval equipment compared to a lawnmower (green bar), including flight operations for an F-18 aircraft. Horizontal lines show the dB(A) levels at which single hearing protection and double hearing protection are required by U.S. Navy regulation. (From Yankaskas, 2009).

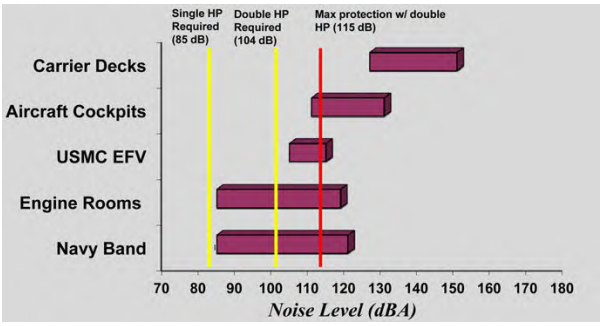

Fig. 3. Horizontal bars show dB(A) range in various U.S. Navy locations, including in the interior of a United States Marine Corps (USMC) Expeditionary Fighting Vehicle (EFV). Yellow vertical lines indicate dB(A) noise levels that require single hearing protection (HP) and double hearing protection. Red vertical line shows the maximum dB(A) level achievable with double hearing protection. (From Yankaskas, 2009).

appropriate HPDs. Clearly, a highly attenuating HPD makes communication a challenge; therefore HPDs with an embedded communication channel would be optimal for military operations. In the near term, greater effort must be made to better identify those individuals who are highly susceptible (or resistant) to NIHL and/or tinnitus. In addition, certain military duties or occupations may increase the risk for developing NIHL and noise-induced tinnitus. Finally, a long term, high risk objective is to regenerate hair cells, nerve fibers and support cells in the cochlea that have been damaged by noise and in so doing restore hearing and suppress tinnitus (Izumikawa et al., 2005; Zheng and Gao, 2000).

In the meantime, there are a number of treatment strategies with varying benefits for dealing with NIHL and tinnitus. Modern hearing aids can provide benefit to compensate for a veteran's hearing loss, loudness recruitment and ability to recognize speech in noise; however, the degree of benefit often depends on the magnitude of hearing loss (Roup and Noe, 2009; Saunders and Griest, 2009; Wilson et al., 2010). The VA's National Center for Rehabilitative Auditory Research (NCRAR) has instituted a five step program called Progressive Audiologic Tinnitus Management (PATM) for the treatment of tinnitus (Henry et al., 2008, 2009).

6. Summary

The personal as well as financial costs associated with tinnitus have increased dramatically in the past decade with the rise of noise levels in the military and civilian life. The impact of tinnitus is seen most dramatically in the billion dollar compensation costs paid to veterans. While efforts at preventing tinnitus and NIHL are clearly important, much more research is needed to understand the biological mechanisms that give rise to tinnitus with the eventual aim of developing effective treatments to silence these phantom auditory sensations that for some are extremely disabling.

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Longitudinal threshold changes in older men with audiometric notches

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Abstract

Age-related hearing loss (presbycusis) is a multifactorial process that results chiefly from the accumulating effects of noise damage and aging on the cochlea. Noise damage is typically evidenced clinically by a discrete elevation (notch) of the auditory thresholds in the 3–6 kHz region of the audiogram whereas aging affects the highest frequencies first. To determine whether the presence of such high-frequency notches influences auditory aging, we examined the 15 year change in audiometric thresholds in 203 men from the Framingham Heart Study cohort. The mean age at the first hearing test was 64 years (range 58–80). Occupational and recreational noise exposure over the 15 years was assumed to be minimal due to the age of the subjects. The presence or absence of a notch was determined using a piecewise linear/parabolic curve fitting strategy. A discrete elevation of the pure-tone thresholds of 15–34 dB in the 3–6 kHz region was deemed a small notch (N1), and elevations of 35 dB or greater were deemed large notches (N2). Absence of a notch (N0) was encoded those ears with < 15 dB elevation in the 3–6 kHz region. The presence and absence of notches correlated with the subjects' history of noise exposure. The 15 year pattern of change in age-adjusted pure-tone thresholds varied significantly by notch category. There was less change over time in the notch frequencies (3–6 kHz) and significantly greater change in the adjacent frequency of 2 kHz in the N2 group as compared to the N0 and N1 groups. The adjacent frequency of 8 kHz showed a significant, but smaller, change in the N1 group as compared to the N0 and N2 groups. The change at 2 kHz was independent of the starting hearing level at E15, whereas the changes at 4–8 kHz were influenced by the hearing level at E15. These data suggest that the noise-damaged ear does not 'age' at the same rate as the non-noise damaged ear. The finding of increased loss at 2 kHz suggests that the effects of noise damage may continue long after the noise exposure has stopped. The mechanism for this finding is unknown but presumably results from prior noise-induced damage to the cochlea.

Key words: Hearing; Noise damage; Aging

1. Introduction

Chronic exposure to excessive (i.e. toxic) noise is an established cause of cochlear damage and hearing loss, and is known as noise-induced hearing loss (NIHL) (NIH Consensus Conference, 1990). The clinical pattern of NIHL from chronic noise exposure is influenced by the characteristics of the noise (e.g. frequency spectrum) and the acoustical transmission characteristics of the ear canal and middle ear. Typically, NIHL begins as a discrete elevation of the pure-tone thresholds in the 3–6 kHz region of the audiogram (Cooper and Owen, 1976). This audiometric pattern is commonly referred to as a 'noise notch', even though some notches may not be due to noise (Gates et al., 1999). The center frequency of notches due to impulse noise from gunfire is 5.9 kHz (Gravendeel and Plomp, 1958), whereas notches due to chronic environmental noise exposure have a lower center frequency, around 4 kHz (Ward et al., 1961). The location of the center frequency of the notch may vary with the resonance frequency of

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the ear canal (Pierson et al., 1994), but ear canal resonance does not fully account for high frequency losses from low-frequency noise (Clark and Bohne, 1978). As the noise exposure continues, the notch deepens and broadens to involve adjacent frequencies (Taylor et al., 1965).

Chronic noise exposure, whether from specific hazardous noise (industrial, recreational) or general environmental noise (sociocusis), is a major component of age-related hearing loss (presbycusis), along with biologic degeneration (aging), and the effects of diseases and toxicity (nosocusis) (CHABA Working Group on Speech Understanding and Aging, 1988). Hearing in people with NIHL, as with people without NIHL, worsens with time, but it is difficult to identify with certainty the relative contributions of noise and aging to the progression of the hearing loss. It is well known that the rate of NIHL decelerates over time, whereas age-related loss accelerates over time with the greatest rate of loss in the highest frequencies and the least loss in the lowest frequencies (Gallo and Glorig, 1964).

Comprehensive estimates of noise-induced permanent threshold shift (NIPTS) and age-related permanent threshold shift (ARPTS) have been developed through the analysis of cross-sectional databases (ISO1999, 1990). These estimates provide a framework in which clinical methods to allocate NIPTS and ARPTS have been developed (Dobie, 1992). However, the biologic processes of auditory aging and the interactions between noise damage and biologic aging are complex and poorly understood (Mills et al., 1997). A key, unresolved issue is whether the aging process is the same in noise-damaged ears as it is in undamaged ears. This is a difficult question to answer given that the basic mechanisms of biologic aging in the cochlea have not been identified, nor have specific clinical markers of biologic aging, as opposed to the effects of disease events, been developed.

Current knowledge and logic suggest that hearing loss due to chronic noise exposure, such as occurs in occupational hearing loss, does not worsen after the noise exposure stops (ACOM Report, 1989). If this is true, then the continued post-exposure changes in the hearing of people with NIHL must be the result of other causes, such as aging or disease. This widely held viewpoint is based on cross-sectional data, i.e. a single measure of the hearing of different people at different ages. A more sensitive and potentially more powerful method to examine this relation is to measure changes in the same people at different times, i.e. a longitudinal analysis.

Examination of the longitudinal changes in auditory thresholds in an unselected, population-based cohort of retirement age and older could provide valuable evidence about the influence of noise damage on auditory aging. The rationale for this approach is two-fold: (a) retired people no longer work in hazardous noise and, (b) older people, in general, have less exposure to recreational and general environmental noise. By excluding nosocusic events through careful screening, the major contributor to the observed longitudinal changes in hearing would be most likely due to aging.

Using data from our longitudinal studies of the hearing of the Framingham Heart Study (FHS) cohort, we sought to determine whether the mean age-adjusted auditory thresholds in male ears with evidence of noise damage change over 15 years to the same degree as in male ears without evidence of noise damage. We reasoned that if the change over time was not different in the two groups, we could conclude that prior noise damage does not influence the accumulation of additional threshold shift with age. However, if the degree of change differed between the two groups, then, logically, some mechanism other than aging must be responsible.

The FHS cohort is a logical choice for this study because: (1) NIHL is common (Gates et al., 1999), (2) audiograms are available from the vast majority of the cohort, and (3) biomedical data are available from all subjects. The prevalence of NIHL in these men is supported by their histories of noise exposure, self-attribution of hearing loss to noise, and characteristic audiometric findings (Gates et al., 1999).

2. Materials and methods

2.1. Subjects

The FHS began in 1948 with a sample, stratified on family size, of 2/3 the families of the city of Framingham in Eastern Massachusetts. The surviving members of the initial sample of 5209 subjects between the ages of 30 and 62 years have been examined for cardiovascular and other disorders every 2 years since (Dawber, 1980). Each biennial examination is identified by a sequential number. Audiometry was done during biennial examinations (E)15 (Moscicki et al., 1985), E18 (Cooper and Gates, 1991) and E22. At each of these examinations, the volunteer subjects had a standard clinical pure-tone audiogram done by a qualified audiologist in accordance with ANSI standards for methods and facilities. Approval for the study of human subjects was given by the review committees at Boston University and the University of Washington.

2.1.1. Exclusions

This report compares the change in audiometric thresholds occurring in the 15 years between FHS examinations E15 and E22. Because large asymmetric dif-

ferences in the mid-range hearing levels (pure-tone average (PTA) of 0.5, 1.0, 2.0 kHz) are unlikely to be due to either aging or noise, those cases with a difference of over 20 dB in the PTA of the right vs. left ears at either the E15 and E22 audiograms were excluded. This criterion excludes obvious unilateral losses due to nosocusic events, such as labyrinthitis and sudden sensorineural hearing loss, as well as Meniere's disease or other unilateral conditions. Only 4.0% of the female subjects in this population had bilateral deep notches. Therefore, the report is limited to the male subjects.

2.2. Variables

The primary outcome variable is the 15 year change in audiometric threshold for each of the eight audiometric frequencies (0.25–8 kHz) for each ear of each subject. The change in pure-tone thresholds was obtained by subtracting the threshold at E22 from the threshold at E15 and was averaged for each of the combined Hz/ear/notch categories. Thresholds at 3 kHz were not measured at E22 because of time constraints; therefore, those threshold values were estimated by interpolation using a parabolic curve fitting algorithm, which is described in Section 2.2.1.

The predictor variables were notch category (0, 1, 2), age, cardiovascular disease (CVD) events (Y/N), smoking history (Y/N) and number of prescription medications used regularly.

2.2.1. Notch detection and characterization

A high-frequency audiometric notch typical of NIHL (noise notch) has three general characteristics: (1) a relatively flat, normal or near-normal, low-frequency threshold profile; (2) a sharply sloping, downward threshold profile in the 2–4 kHz area; and (3) a flat or upsloping threshold profile in the 6–8 kHz area. (Cooper and Owen, 1976)

We used a validated novel mathematical method to detect threshold patterns meeting the above criteria (Gates et al., 1999). The method employs a piecewise linear/parabolic least-squares curve fitting algorithm. This algorithm provides a rapid and reproducible method for notch identification and measurement. Such a method reduces the 'noise' of threshold variations due to test–retest variability. The details of this method are described next.

Mathematically, the goal is to fit a low-dimensional curve (for example, a straight line) to the set of observed data points that form the audiometric threshold plot. The observational question arises as to how to choose the parameters of the curve that provide the closest fit to the data. The closeness of the fit is defined as the square of the deviation of each individual point from the given curve summed over all data points.

Denoting the audiometric data points by x_i = frequency (in Hz) and y_i = sound pressure level (in dB HL) of the ith data point for $i = 1,...N$, and choosing a function $f(x)$ to fit the data, the closeness c of the fit is given as:

$$c = \sum_{i=1}^{N} (y_i - f(x_i; p))^2$$

A variable p has been introduced as an additional argument of the function $f(x)$ to denote a set of parameters, such as slope, curvature, etc., that describes the shape of the function. To find the closest fit, we then need to minimize the quantity c by adjusting the set of parameters p. This type of optimization problem is known as a least-squares problem.

The choice of the function $f(x)$ is based on the shape of the audiogram. The threshold data of subjects without NIHL are expected to decay linearly at a variable rate as frequency increases. However, the threshold plot of subjects with NIHL will show a notable notch at higher frequencies in an otherwise linear decay. The depth and location of the notch as well as the slope of the straight line vary from subject to subject and depend on various factors such as age and extent of noise exposure.

The typical data structure of audiograms suggested that a two-part function would be appropriate: one modeling the linear decay of sound pressure with frequency and one modeling the notch. Since the shape and location of the notch varies, the data were split into two subsets. The first subset was fitted to a straight line and the second subset was fitted to a parabola. The closeness of fit is then given as:

$$c = \underbrace{\sum_{i=1}^{M} (y_i - (mx_i + b))^2}_{\text{linear fit}} + \underbrace{\sum_{i=M}^{N} (y_i - (Ax_i^2 + Bx_i + C))^2}_{\text{parabolic fit}}$$

where M denotes the Mth data point. We then need to minimize the closeness of fit by adjusting the free parameters (m, b, A, B, C) of the two curves as well as by adjusting the point M at which the switch from a linear to a parabolic curve is made. The last data point (i.e. the highest frequency) is not included in the parabolic fit if a downward slope is detected in the highest frequency.

2.2.2. Selection rules for notch detection

Once the optimal parameters (m, b, A, B, C) have been determined, it is possible to work with a continuous representation of the data rather than the discrete set of data points. A set of selection rules was developed to distinguish a notch in the data from an otherwise parabolic fit. The following two rules result in a

correct classification of audiograms. A notch in the data is detected when:

$$A > 0, \text{ and} \quad (1)$$

$$2000 \leq f_y \leq 8000 \quad (2)$$

where f_y stands for the frequency at the extreme of the parabola. In some instances, the decay of intensity for higher frequencies is better approximated by a convex parabola rather than a straight line. The first condition addresses this case and, in the case of the notch, ensures the concave nature of the parabolic fit. The second rule is empiric and limits the frequency corresponding to the lowest point of the parabola to frequencies ranging from 2000 to 8000 Hz. The application of these rules to three typical audiometric data plots is shown in Fig. 1. In Fig. 1A, the parabolic fit is a straight line so that $A = 0$, which in rule 1 indicates that a notch is not present. In Fig. 1B,C, $A > 0$ and point Y falls in the frequency range specified by rule 2 so that a notch is deemed to be present.

2.2.3. Characterization of the notch

After successfully fitting the piecewise linear/parabolic curve to the data and identifying a notch according to the above rules, the notch was quantified according to the depth of the notch in dB from the transition point X to the apogee of the parabola. Hence, the notch depth is expressed as a difference in dB between point Y and point X (Fig. 1), not as the absolute value of point Y. The central frequency of the notch maximum and the breakpoint where the linear and parabolic functions intersect permit the calculation of the notch width. The width of the notch (a) and the depth of the notch (b) are used to determine the aspect ratio of the notch (a/b).

Each ear of each subject was labeled as having no notch (N0), a small notch (N1) or a large notch (N2) using the notch depth cut-points of 15 dB (N0/N1) and 35 dB (N1/N2) (see Fig. 2). The rationale for the choice of these values is as follows: (a) 15 dB is an unambiguous audiometric threshold difference that is highly unlikely to be due to test–retest variability; and (b) 35 dB

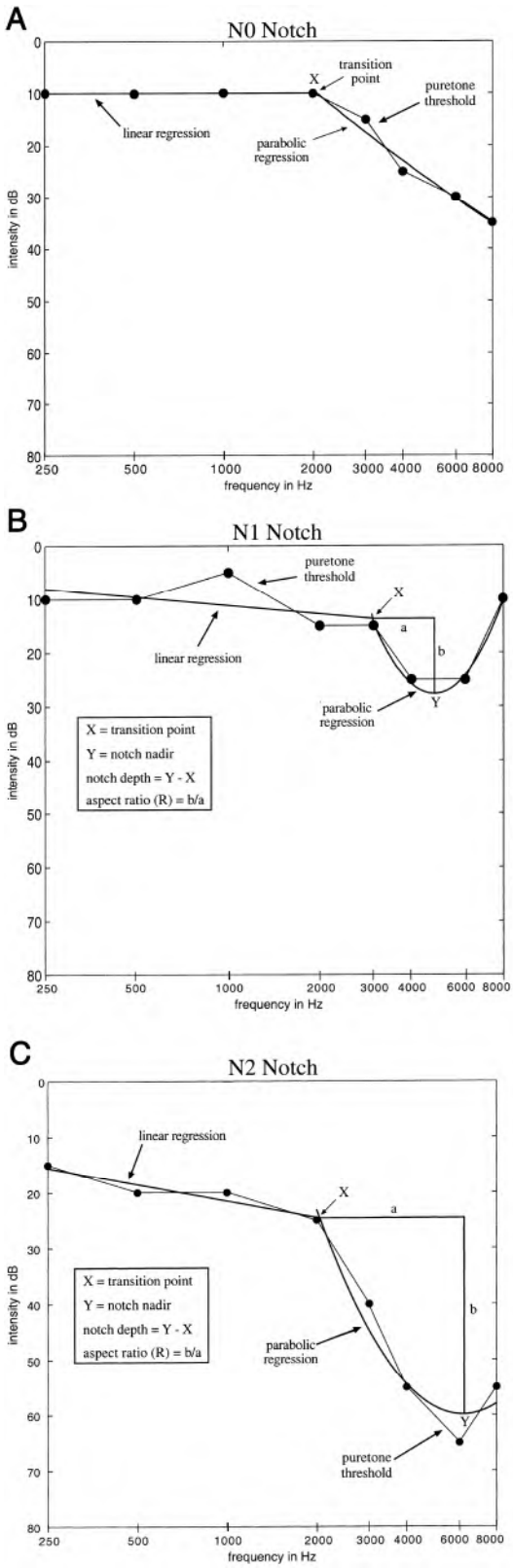

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Fig. 1. The relation between the raw thresholds and the regression lines (linear and parabolic) is shown for an N0 case (A: no notch), an N1 case (B: small notch) and an N2 case (C: deep notch). The transition point (X) indicates the junction between the linear and parabolic curve fits. Point Y indicates the nadir of the parabola and the difference ($Y-X$) indicates the depth of the smoothed notch. The aspect ratio of a and b determines whether the notch is vertically ($b > a$) or horizontally ($a > b$) oriented. A case is coded as a large notch (N2) when $b \geq a$ and $Y-X \geq 35$ dB, or as a small notch (N1) when $b \geq a$ and $Y-X \geq 15$ dB < 35 dB. Cases are coded as N0 if $a > b$ or $Y-X < 15$ dB.

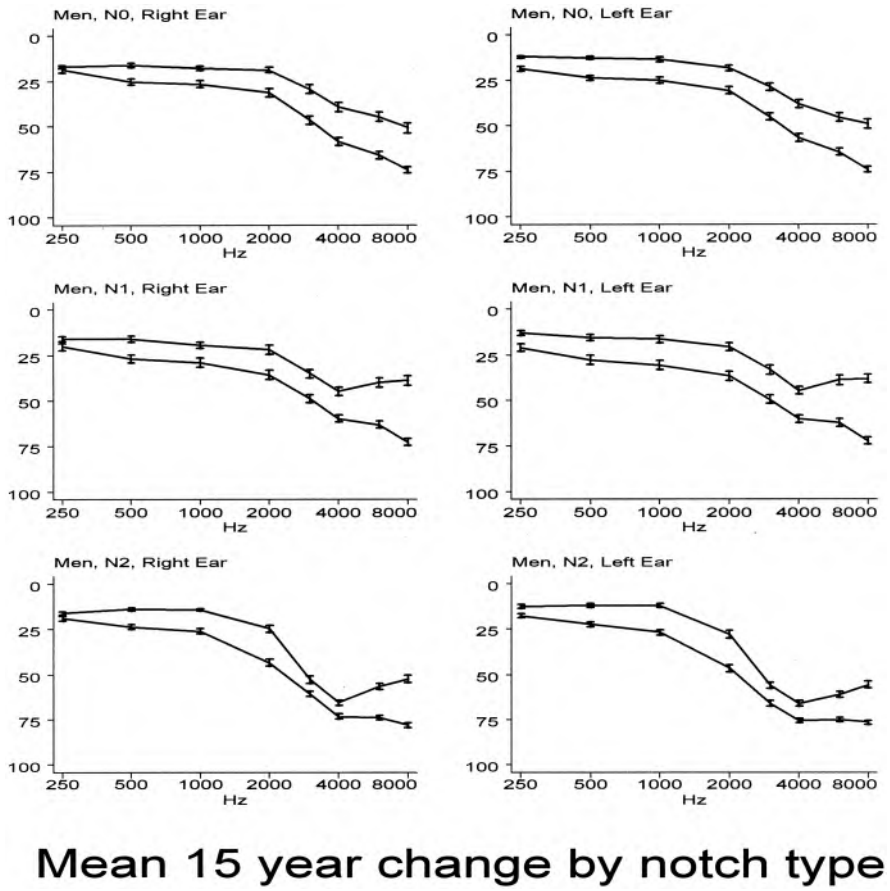

Fig. 2. The mean ± S.E.M. values for pure-tone thresholds are shown separately for the right and left ears of the subjects group by notch group (N0: no notch, N1: small notch, N2: large notch) and examination. The upper curve denotes the group mean thresholds at E15 and the bottom curve the group mean thresholds 15 years later at E22.

was the mean notch depth in the subjects who had a notch of >15 dB. These cut-points divide the cases into three groups based on the severity measure of notch depth. These categories are operationally defined as: (a) minimal or no evidence of noise damage (N0, notch depth = 0–15 dB), (b) possible noise damage (N1, notch depth >15 dB, <35 dB) and, (c) probable noise damage (N2, notch depth ≥ 35 dB). To also qualify as a notch, the aspect ratio of the depth to the width of the notch had to be 0.5 or greater, which excludes broad, shallow notches unlikely to be due to NIHL. The audiometric patterns were inspected visually to verify appropriate categorization.

2.2.4. Biomedical variables

The FHS database contains a record for each subject at each examination of CVD events (Y/N), smoking history (Y/N) and number of prescription medications used regularly. CVD events were noted over the lifetime of the subject whereas smoking and prescription medication use were limited to the 15 year interval between E15 and E22.

2.3. Analysis

The primary analysis was done to determine if the presence of audiometric notches at E15 influenced the 15 year mean change in age-adjusted hearing thresholds. The secondary analysis was done to determine if the 15 year mean change rate was also influenced by starting hearing level, or by CVD events, smoking or chronic use of medications to control blood pressure. Each of the latter three secondary covariates is an established risk factor for age-related hearing loss (Cruickshanks et al., 1998; Gates et al., 1993; Lee et al., 1998).

Descriptive statistics used mean values and employed the Chi-square test to assess the relation between notch category to gender and ear, the *t*-test for comparison of rate of change by ear, and analysis of variance

Table 1
Distribution of audiometric notches at E15 by ear

Notch	Number (%)		Age (years)
Category	RE	LE	
N0	75 (37)	68 (34)	63
N1	50 (25)	47 (23)	64
N2	78 (38)	88 (43)	64
Totals	203 (100)	203 (100)	64

(ANOVA) to determine the relation between notch and age-adjusted threshold change by frequency.

Multivariate covariance analyses were performed for each ear, adjusting for age, smoking status, prevalent CVD and anti-hypertensive medication to evaluate the 15 year change in hearing threshold for each frequency as the outcome variable and notch category as the predictor variable. Then, a further multivariate analysis was performed that combined right and left ears by notch level. To adjust for multiple comparisons, the Bonferroni adjustment ($P < 0.05$) was used.

3. Results

The audiograms of all 242 men who had hearing tests at both E15 and E22 were available for this study. The average interval between tests was 15 years. Fourteen asymmetric cases (5.8%) at E15 and 25 additional cases (10.9%) that became asymmetric at E22 were excluded, leaving 203 cases for analysis. There was no relation of asymmetry to notch (N) category. The average age and S.D. at the first hearing test was 64.1 ± 4.3 years with a range of 58–80 years. The mean age ± S.D. at the second test was 78.5 ± 4.5 years. Given a usual retirement age of 65 or earlier for tradesmen, it is presumed but not documented that occupational noise exposure ceased for the vast majority of subjects at or about the time of E15 and that there was no substantial continuing toxic noise exposure, including recreational noise, between E15 and E22.

3.1. Description of notches

The distribution of notches at E15 by ear is shown in Table 1. There were slightly more notches in left ears than in right ears, but this difference was not significant. Notch depth did not vary by age of the subjects (ANOVA, $P = 0.588$). The mean hearing threshold levels by notch category at E15 and E22 are shown in Fig. 2. In 54% of cases, the notch categories were the same in both ears: bilateral N0 in 27%, bilateral N1 in 9% and bilateral N2 in 18%. In 16% of cases, there was a deep (N2) notch in one ear and no notch (N0) in the opposite ear. In the remaining 30% of cases, the notch category differed by one step between ears.

3.2. Primary analysis: 15 year change in pure-tone thresholds

The frequency-specific 15 year differences were found to be normally distributed in all cases. There was a significant difference in the amount of change in the thresholds by ear and test frequency. The left ear changes were significantly greater than the right ear in the lower frequencies (0.25–2 kHz), but the threshold changes for the higher frequencies (3–8 kHz) did not differ by ear. The magnitude of the 15 year threshold

Table 2
Mean 15 year threshold shift by ear, frequency and notch depth category

	Test frequency (kHz)							
	0.25	0.5	1	2	3	4	6	8
Men: right ears (dB)								
Notch 0	1.8	9.1	8.7	12.5	17.2	19.0	21.2	23.1
Notch 1	4.0	11.0	9.7	14.0	14.0	14.8	22.8	33.3
Notch 2	2.9	9.9	11.9	18.7	10.5	7.8	17.5	25.6
P value[a]	0.530	0.5861	0.1707	0.0043*	N.A.	0.0001*	0.0570	0.0020*
Men: left ears (dB)								
Notch 0	6.5	11.0	11.2	12.4	16.2	18.4	18.5	25.3
Notch 1	7.9	12.3	14.3	16.0	16.6	16.0	23.6	33.3
Notch 2	4.9	10.5	14.6	18.8	10.0	9.5	14.1	20.9
P value[a]	0.2289	0.5387	0.1123	0.0018*	N.A.	0.0001*	0.0001*	0.0001*
Men: both ears (dB)								
Notch 0	4.1	10.0	9.9	12.4	16.7	18.7	19.9	24.2
Notch 1	5.9	11.6	11.9	14.9	15.2	15.4	23.2	33.3
Notch 2	4.0	10.2	13.3	18.7	10.3	8.7	15.7*	23.1
P value[a]	0.3144	0.3854	0.0188*	0.0001*	N.A.	0.0001*	0.0001*	0.0001*

[a]ANOVA adjusted for age, smoking, medication and CVD.
*Significant by Bonferroni adjustment ($P < 0.05$).

change varied with the level of the threshold at E15 for the higher frequencies (3–8 kHz) but was independent of starting threshold level for the lower frequencies (0.25–2 kHz).

The magnitude of the 15 year threshold change by frequency and by ear is shown by notch category in Table 2. The significance level of threshold change across the three notch groups was assessed separately for each Hz/ear combination, except for the 3 kHz differences which were estimated.

As can be seen in Table 2, the patterns of threshold change varied with frequency. At 0.25–1 kHz, there was no difference across the notch groups. For 2 kHz, there was an increasing threshold shift across the increasing notch groups. For 4 kHz, there was a decelerating threshold shift across the increasing notch groups. The pattern at 6 kHz was also decelerating but the magnitude was less than at 4 kHz. At 8 kHz, there was a variable pattern across the three notch groups showing accelerating loss from N0 to N1 and a decelerating loss from N1 to N2.

Because these patterns of change did not differ by ear, we display the difference in thresholds for all ears of all subjects by notch groups in Fig. 3 to facilitate further comparisons.

The expected no difference pattern in the low frequencies was not analyzed further. The three remaining patterns were evaluated with Bonferronni's method to determine which of the three between-group comparisons was significant. In both the accelerating and decelerating patterns, the statistically significant difference was between ears with large notches (N2) and those with no notch (N0), whereas in the variable pattern (8 kHz), the statistically significant differences were between the N1 and either the N0 or N2 groups.

3.3. Secondary analyses

3.3.1. Hearing level at E15

The primary ANOVA comparisons were repeated with the addition of threshold level at E15 as a covariate. In all the test frequency comparisons, except for 2 kHz, the statistical effect of notch became non-significant and initial threshold level was significant (data not shown). At 2 kHz, for both ears, notch category remained highly significant after adjustment for age and initial threshold level with P values of < 0.001.

3.3.2. Biomedical covariables

Multivariate covariance analyses were performed for

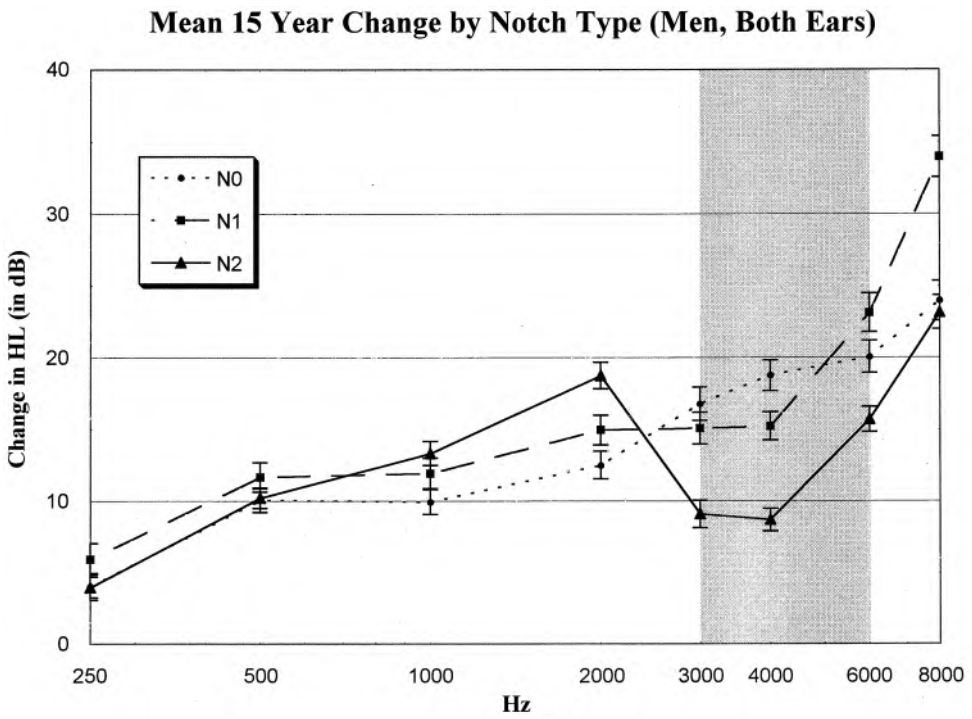

Fig. 3. The curves show the 15 year change in mean ± S.E.M. auditory thresholds for the three notch groups for right and left ears combined. There is a significantly lower rate of change for 3–6 kHz thresholds in the N2 group as compared to the N0 group, and a significantly higher rate of change at 1 kHz and 2 kHz for the N2 group compared to the N0 group. The change at 8 kHz is greater for the N1 group than the N0 or N2 groups.

each ear, adjusting for age, smoking status, prevalent CVD and anti-hypertensive medication to evaluate the 15 year change in hearing threshold for each frequency group as the outcome variable and notch category as the predictor variable. Then, a further multivariate analysis was performed that combined right and left ears by notch level using Bonferroni's correction to adjust for multiple comparisons. The results from the above analyses support the primary analysis results and confirmed that the difference values (0.25–8 kHz) were not affected by the covariables: smoking status, prevalent CVD and anti-hypertensive medication (data not shown).

4. Discussion

These analyses indicate that the change in hearing thresholds with time in male ears with deep audiometric notches differs from that of male ears without such notches. By excluding nosocusic events and noise as potential contributors to the change in hearing with time, these changes are most likely due to intrinsic factors within the cochlea. How can we account for the different findings in the N2 vs. the N0 cases?

The reduced rate of change over time in the frequencies encompassed by the notch (3–6 kHz) reflects the well known asymptotic, decelerating pattern of change over time in noise-damaged ears (Gallo and Glorig, 1964). Simply stated, hair cells lost from one cause cannot be 're-lost' from another cause. In this example, the first cause is noise damage and the other cause is 'aging' of the ear. Thus, one would expect less change over time in the thresholds of the frequencies subserved in the damaged area of the cochlea, which is precisely what was observed.

The finding of an accelerated rate of loss over time in the frequency areas adjacent to the deep noise notch is a new finding. This accelerated loss was most apparent at 2 kHz and was independent of the age of the subjects and the degree of prior loss. A similar but less impressive accelerated loss also occurred at 8 kHz in the ears with a small notch.

We postulate that in ears with substantial prior noise damage, the cochlear architecture and/or function were altered in such a way to foster continuing worsening of hearing sensitivity over time in the adjacent areas. One possible explanation for this phenomenon is based on the recent finding that potassium ions are recycled in the cochlea through an elaborate transcellular system involving the outer hair cells, supporting cells and the spiral ligament cells (Spicer et al., 1998). It may be the case that the regions of the cochlea adjacent to damaged areas experience potassium toxicity because the damaged hair cells can no longer recycle potassium in the transduction process. Bohne and Rabbit (Bohne and Rabbitt, 1983), in noting acute ultrastructural communications between endolymph and perilymph in noise-damaged cochleae, also suggested that fluid mixing and potassium toxicity might contribute to continued damage in the cochlea. Other mechanisms may be involved as well.

Although this study cannot determine the mechanism for the accelerated loss observed in this analysis, it is clear that the noise-damaged ear does not 'age' at the same rate as the ear without evidence of noise damage. This finding calls into question assumptions based on cross-sectional data that have been made about the relative contributions of ARPTS and NIPTS. Cross-sectional data would over-estimate the threshold shift due to aging because the accelerated time-related degeneration observed in the N2 ears would have been attributed to aging rather than to the prior noise damage. We suggest that the accelerated loss at 2 kHz is a progression of the noise damage in the absence of continuing noise exposure. Of interest, Taylor et al. noted a similar delayed worsening of the 2 kHz thresholds in the jute weavers after 30 years of exposure (Taylor et al., 1965).

5.1. Caveats

We recognize that a 'noise notch' is not prima facie evidence of noise damage. Nonetheless, it is highly likely that all the ears with substantial NIHL had deep notches. The possible inclusion of a small but unknown number of ears with a notch not due to noise might increase the variability of these findings but it is very unlikely that there would be sufficient numbers to weaken the conclusions of the analyses. Of interest, the ears with a small notch tended to change over time in a pattern similar to the ears without a notch. Given the absence of a clinical guideline for the diagnosis of a noise notch and the characteristic audiometric pattern of NIHL observed in these subjects, we believe the criteria for categorizing a notch in this report are clinically valid.

These findings apply to the 15 year span in people from 58 to 83 years at the first hearing test and 72–95 years at the second test, and should not be extrapolated to other age groups or time spans.

Lack of documentation that hazardous noise exposure ceased between E15 and E22 is a weakness of this report. The presumption that occupational noise exposure ceased is based on the usual retirement age of 60–65 for most workers. A further assumption is made that hazardous recreational noise exposure is uncommon in older people, as common experience indicates that older people generally lead quieter lives than younger people.

Acknowledgements

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ON HEARING

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World report on hearing

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CONTENTS

CAUSATIVE FACTORS:
Exposure to loud sounds and loud noise

Exposure to loud sounds puts children and adults at risk not only of hearing loss, but other noise-induced health problems, such as insomnia and cardiovascular illnesses *(64)*. Typically, sound intensity[5] above 80 dB, heard for periods longer than 40 hours a week can lead to hearing loss by damaging the sensory hair cells within the inner ear *(82)*. The higher the level of sound and the longer the duration, the greater the risk of hearing loss *(82, 106)*.[6]

Loud sounds can be encountered in the workplace, in the overall living environment, and are commonly experienced as part of recreational activities. Situations which present a risk of hearing loss include:

- **Occupational settings**: High levels of occupational noise remain a problem in all regions of the world *(77)*. In the United States of America (USA), for example, more than 30 million workers are exposed to hazardous noise *(87)*. The European Agency for Safety and Health at Work[7] estimates that 25–33% of the workforce in Europe is exposed to high-level noise at least a quarter of their working time *(75)*. In other parts of the world, data on noise-induced hearing loss are scarce, but available evidence suggests that average noise levels are well above the recommended levels *(77, 107)* and may well be rising due to increasing industrialization that is not always accompanied by protection.

  Workers in shipbuilding, the armed forces, the engineering industry, manufacturing, building and construction, woodworking foundries, mining, the food and drink industry, agriculture and entertainment are most likely to be exposed to high levels of sound *(74–76)*. Concurrent vibration or exposure to chemicals (e.g. solvents, lead) enhances the harmful effects of noise on hearing.

Noise in sporting events can reach levels as high as 135dB

- **Recreational settings**: Risk of hearing loss is also encountered when people expose themselves to loud levels of sound in recreational settings *(79)*. Noisy leisure activities, especially the use of firearms, can cause the same damage to hearing as exposure to occupational noise *(74)*. Prolonged listening to loud music through personal audio devices (i.e. personal music players used

[5] Sound intensity is measured in decibels, represented as "dB".

[6] The equal energy principle states that the total effect of sound is proportional to the total amount of sound energy received by the ear, irrespective of the distribution of that energy over time and that the amount of energy doubles for every 3 dB increase in intensity of sound.

[7] See: https://osha.europa.eu/en.

with headphones/earphones) increases the risk of hearing loss and results in worsening of audiometric thresholds *(80)*. Listeners who regularly use portable audio devices can expose themselves to the same level of sound in 15 minutes of music at 100 dB that an industrial worker would receive in an 8-hour day at 85 dB. Given that the volume range of a typical listener is between 75 dB and 105 dB *(64)*, this presents cause for concern. WHO estimates that over 50% of people aged 12–35 years listen to music over their personal audio devices at volumes that pose a risk to their hearing. Among those who frequently visit entertainment venues, nearly 40% are at risk of hearing loss *(84)*.

- **Environmental factors** (other than occupational and recreational settings): Loud sounds are encountered routinely in the everyday environment. Common examples include the noise from traffic or home appliances. Overall, environmental exposure to noise is mostly lower than the levels required for development of irreversible hearing loss. However, people exposed to such levels of noise (not sufficient to cause hearing loss) can experience other health effects, including greater risk of ischaemic heart disease, hypertension, sleep disturbances, annoyance and cognitive impairments *(81, 82)*.

CASE STUDY

Loud sounds can cause lasting damage

Matt Brady, a 22-year-old University student suffered permanent hearing damage from listening to music at a very high volume while exercising on a treadmill.

It is estimated that in the USA, 21 million adults (19.9%) who reported no exposure to loud or very loud noise at work showed evidence of noise-induced hearing loss *(108)*.

Just as on a regular day, Matt was exercising and listening to music using his earphones when he experienced pain in his ears and head, followed by lasting hearing loss which affected his social and academic life. It took almost a year for multiple consulting doctors to understand the association between his hearing loss and his habit of listening to loud music. Matt now has permanent difficulty in listening and finds conversation challenging in situations with background noise.

Having learnt the hard way, Matt Brady is now a passionate advocate for safe listening behaviour as a way of ensuring others do not experience a similar impact to their hearing *(109)*.

- **Development of noise-induced hearing loss:** It is well established that noise damages the structures within the cochlea in a dose-response manner – i.e. the higher the amount of exposure, the greater the impact *(83, 84)*. Sometimes,

such damage may manifest only as difficulty in understanding speech in a noisy environment – a typical complaint associated with noise-induced hearing loss *(55)*. In addition, noise exposure is commonly associated with tinnitus – the sensation of ringing in the ear, and the phenomenon known as "hidden hearing loss" *(85)*.

- ***Tinnitus***: is derived from the Latin verb tinnire (to ring) and refers to the conscious perception of an auditory sensation in the absence of a corresponding external stimulus *(110)*. Tinnitus is commonly an outcome of noise exposure and may accompany or occur in the absence of clinically evident hearing loss *(85)*. Research shows that workers exposed to noise are more likely to experience tinnitus *(83)*.

  Tinnitus may also be caused by other auditory and nonauditory conditions. The onset, perception, and impact of tinnitus can be influenced by a number of psychological factors, such as anxiety and depression *(111)*. Prevalence in the general population ranges from 5.1% to 42.7%, while bothersome tinnitus is encountered in 3–30% of the population *(112)*.

- ***Hidden hearing loss***: refers to the condition where an individual experiences common symptoms associated with noise-related auditory damage such as difficulty in hearing noise, tinnitus, and hyperacusis. However, as its name suggests, hidden hearing loss (HHL) is undetectable on pure tone audiometry, which shows normal hearing sensitivity at 250–8000 Hz. The condition is attributed to the destruction of synaptic connections between hair cells and cochlear neurons (cochlear synaptopathy) which occurs well before the hair cells are damaged and as a result of exposure to noise *(85, 113)*. It is likely that many people struggle with HHL and that it occurs in younger age groups due to increasing exposure to recreational noise *(85)*. It is also suggested that the changes caused by noise exposure, even early in life, make the ears significantly more vulnerable to ageing and hasten the onset of age-related hearing loss *(86)*.

  Irrespective of its presentation, the progression of irreversible noise-related auditory damage is relentless so long as the exposure continues.

CASE STUDY

Studying the long-term impact of sound exposure: The Apple Hearing Study*

To better understand long-term sound exposure and its impact on hearing health, a large-scale study was launched in 2019 through collaboration between the University of Michigan, USA and Apple.** The outcomes of this study will help guide public health policy and prevention programmes designed to protect and promote hearing health both in the USA and globally.

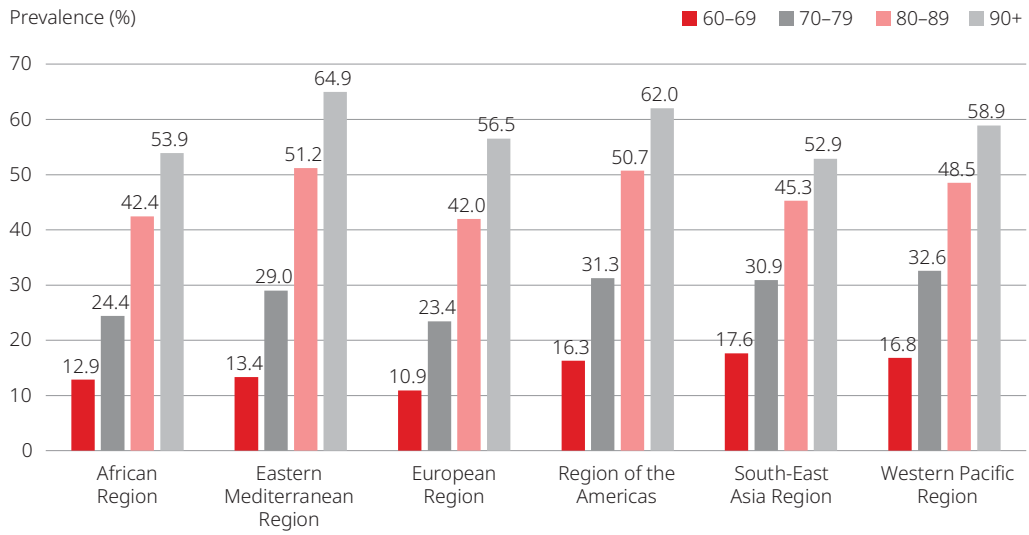
* https://sph.umich.edu/applehearingstudy/

**https://clinicaltrials.gov/ct2/show/NCT04172766

CAUSATIVE FACTORS:
Age-related factors

Given its high prevalence in the community, age-related hearing loss (ARHL) – also known as presbycusis – poses the greatest societal and economic burden from hearing loss across the life course and is expected to increase with the current demographic shifts (see Section 3). Current estimates suggest that over 42% of people with any degree of hearing loss are aged above 60 years. Globally, the prevalence of hearing loss (of moderate or higher grade severity) increases exponentially with age, rising from 15.4% among people aged in their 60s, to 58.2% among those aged more than 90 years. This trend is observed across all WHO regions. Figure 1.4 below shows a prevalence across regions of 10.9–17.6% among individuals aged 60–69 years, increasing to 41.9–51.2% among those aged 80–89 years, and reaching 52.9–64.9% in those aged above 90 years.

Figure 1.4 Prevalence of hearing loss (of moderate or higher grade) in older adults by decades



The development of ARHL can be attributed to physical and environmental insults, combined with genetic predispositions, and an increased vulnerability to physiological stressors and modifiable lifestyle behaviours experienced throughout the course of life *(6).* These factors include exposure to loud noise, ototoxic medications or chemicals, smoking, and dietary habits, as well as chronic conditions, such as cardiac disease. While factors causing ARHL in an individual cannot be separated, the additive nature of such insults, combined with biological susceptibilities, increase the risk of hearing loss. Adopting preventive behaviours, as outlined earlier, and making healthy lifestyle choices in the form of good nutrition, exercise and the avoidance of smoking, can reduce risk of hearing loss in older age.

The impacts of unaddressed adult onset hearing loss include social withdrawal, lost productivity from early retirement and the costs of informal care, mental and physical declines *(114–117)*. Without timely intervention, ARHL is associated with poorer quality of life as well as a broad range of negative effects on the communication partners of those affected *(118)*. Preventive efforts, as described below, are supported by strong public health strategies (outlined in Section 2) and can reduce the occurrence of ARHL. In addition, early detection of hearing loss, and appropriate interventions to address ARHL can mitigate many of the associated adverse effects *(119–121)*.

1.2.3 PROTECTIVE AND PREVENTIVE FACTORS OF HEARING LOSS

Various factors and interventions can either prevent or address the above-mentioned causes and thereby prevent onset of hearing loss or delay its progression. Detailed information on ear and hearing care (EHC) practices that can prevent ear diseases and maintain hearing capacity is provided below. The most relevant preventive actions that can be undertaken by individuals at a personal level across the life course to maintain their own hearing capacity is set out in Table 1.2 *(122–124)*. Preventive public health actions, not included in the table, are described in Section 2 of this report.

> More than 1.5 billion people experience some degree of hearing loss, which can significantly impact their lives, their families, society and countries.

1.3 DECLINE IN HEARING CAPACITY

1.3.1 DEFINITION AND TYPES OF HEARING LOSS *[148]*

A person is said to have hearing loss if their hearing capacity is reduced and they are not able to hear as well as someone with normal hearing. "Normal" hearing typically refers to hearing thresholds of 20 dB or better in both ears (see Table 1.3).

Those with a hearing threshold above 20 dB may be considered "hard of hearing" or "deaf" depending upon the severity of their hearing loss. The term "hard of hearing" is used to describe the condition of people with mild to severe hearing loss as they cannot hear as well as those with normal hearing. The term "deaf" is used to describe the condition of people with severe or profound hearing loss in both ears who can hear only very loud sounds or hear nothing at all.

Different types of hearing loss include:

- *Conductive hearing loss*: This term is used when hearing loss is caused by problems located in the ear canal or the middle ear which make it difficult for sound to be "conducted" through to the inner ear.
- *Sensorineural hearing loss*: This term is used when the cause of hearing loss is located in the cochlea or the hearing nerve, or sometimes both. "Sensori-" relates to the cochlea which is a "sense organ"; "neural" relates to the hearing nerve.
- *Mixed hearing loss*: This term is used when both conductive and sensorineural hearing loss are found in the same ear.

1.3.2 ASSESSING HEARING CAPACITY

Hearing capacity refers to the ability to perceive sounds and is commonly measured through pure tone audiometry (PTA) – considered the gold standard test of assessment. Audiometric threshold shifts help to define the nature of hearing loss, which may be conductive, sensorineural or mixed in type; and range from mild to complete in severity.

Assessment of hearing capacity through PTA is essential, both for epidemiological purposes and to guide rehabilitation. However, PTA assessment should not be the sole determinant for rehabilitation, mainly because audiometric shifts do not provide information on how sounds are processed by the central auditory system, and therefore offer only limited insight into "real-world" functioning *(149)*. For example, a person with an audiogram[8] test result of "normal" may face problems in difficult listening environments, such as in noisy situations *(85, 150)*. Even when hearing loss is mild and therefore may not be considered significant, a person may experience limitations in everyday functioning which would not be reflected through the sole assessment of an audiogram *(151, 152)*. Children and adults may have a normal audiogram but have a deficit in processing auditory information in the brain and limitations in hearing – referred to as central auditory processing disorder *(149, 153)*. Some of these limitations can be addressed through speech tests such as "speech discrimination" and "speech-in-noise" tests *(149)*. It is therefore important to take a holistic view of a person's audiological profile and hearing experiences to ensure that limitations in activity, participation in quiet and noisy environments, and communication needs and preferences, are all addressed *(8, 154)*. These considerations are elaborated in Section 2.

1.3.3 AUDITORY PROCESSING DISORDERS

Some children and adults may experience hearing difficulties in the absence of any substantial audiometric findings. These may have an auditory processing disorder (APD) – a generic term for hearing disorders that result from the poor processing of auditory information in the brain *(149, 153)*. This may manifest as poor hearing and auditory comprehension in some circumstances, despite normal hearing thresholds for pure tones. Prevalence estimates of APD in children range from 2–10% with frequent co-occurrence in children with other learning or developmental disabilities *(153, 155)*. APD can affect psychosocial development, academic achievement, social participation, and career opportunities. Age-related APD is also a common contributor to hearing difficulties in older age.

1.3.4 GRADES OF HEARING LOSS

To standardize the way in which severity of hearing loss is reported, WHO has adopted a grading system based on audiometric measurements. This system is a revision of an earlier approach adopted by WHO, and differs from the earlier system in that measurement of onset of mild hearing loss is lowered from 26 dB to 20 dB; hearing loss is categorized as mild, moderate, moderately-severe, severe, profound or complete; and unilateral hearing loss has been added. In addition to the classifications, the revised system provides a description of the functional

[8] Audiograms show the minimum intensity, in decibels, a person can hear at different frequencies of sound. This is typically depicted in graph form following a hearing test, as measured by an audiometer.

consequences for communication that are likely to accompany each level of severity *(148)*. This revised grading system is presented in Table 1.3 below.

Table 1.3 Grades of hearing loss and related hearing experience*

Grade	Hearing threshold‡ in better hearing ear in decibels (dB)	Hearing experience in a quiet environment for most adults	Hearing experience in a noisy environment for most adults
Normal hearing	Less than 20 dB	No problem hearing sounds	No or minimal problem hearing sounds
Mild hearing loss	20 to < 35 dB	Does not have problems hearing conversational speech	May have difficulty hearing conversational speech
Moderate hearing loss	35 to < 50 dB	May have difficulty hearing conversational speech	Difficulty hearing and taking part in conversation
Moderately severe hearing loss	50 to < 65 dB	Difficulty hearing conversational speech; can hear raised voices without difficulty	Difficulty hearing most speech and taking part in conversation
Severe hearing loss	65 to < 80 dB	Does not hear most conversational speech; may have difficulty hearing and understanding raised voices	Extreme difficulty hearing speech and taking part in conversation
Profound hearing loss	80 to < 95 dB	Extreme difficulty hearing raised voices	Conversational speech cannot be heard
Complete or total hearing loss/deafness	95 dB or greater	Cannot hear speech and most environmental sounds	Cannot hear speech and most environmental sounds
Unilateral	< 20 dB in the better ear, 35 dB or greater in the worse ear	May not have problem unless sound is near the poorer hearing ear. May have difficulty in locating sounds	May have difficulty hearing speech and taking part in conversation, and in locating sounds

* The classification and grades are for epidemiological use and applicable to adults. The following points must be kept in mind while applying this classification:

- While audiometric descriptors (e.g. category, pure-tone average) provide a useful summary of an individual's hearing thresholds, they should not be used as the sole determinant in the assessment of disability or the provision of intervention(s) including hearing aids or cochlear implants.
- The ability to detect pure tones using earphones in a quiet environment is not, in itself, a reliable indicator of hearing disability. Audiometric descriptors alone should not be used as the measure of difficulty experienced with communication in background noise, the primary complaint of individuals with hearing loss.

Unilateral hearing loss can pose a significant challenge for an individual at any level of asymmetry. It therefore requires suitable attention and intervention based on the difficulty experienced by the person.

‡ "Hearing threshold" refers to the minimum sound intensity that an ear can detect as an average of values at 500, 1000, 2000, 4000 Hz in the better ear *(148, 156, 157)*.

A-226-14
2015 FCA 119

Anne Cole (*Appellant*)

v.

Attorney General of Canada (*Respondent*)

Indexed as: Cole v. Canada

Federal Court of Appeal, Gauthier, Ryer and Webb JJ.A.—Ottawa, February 25 and May 5, 2015.

Veterans — Appeal from Federal Court decision dismissing judicial review of Veterans Review and Appeal Board decision refusing to grant appellant's application for disability pension pursuant to Pension Act, s. 21(2)(a) for claimed condition of major depression — Appellant's military career ending when appellant medically discharged on account of four major conditions, including major depression — Appellant applying to Department of Veterans Affairs (DVA) for disability pension in respect of military service — Under Act, s. 21(2)(a), applicant must establish causal connection between claimed condition, military service to be granted disability pension — Board's record indicating that appellant's depression traced to factors relating to appellant's military service (military factors), to personal life (personal factors) — Board rejecting appellant's application for disability pension given appellant's failure to establish that military factors causing or aggravating her claimed condition — Federal Court determining that Board's weighing of evidence, interpretation of statutory scheme reviewable on standard of reasonableness — Concluding that Board interpreted "arose out of" in Pension Act, s. 21(2)(a) as requiring appellant's military service to be "primary or major cause" of depression; then finding that Board making no reviewable error in using that interpretation — Whether Federal Court erring in selecting reasonableness as standard of review regarding interpretative issue; what was correct interpretation of causal connection requirement of phrase "arose out of or was directly connected with" in Pension Act, s. 21(2)(a); whether Board's primary cause interpretation of causal connection requirement of phrase "arose out of or was directly connected with" in Act, s. 21(2)(a) unreasonable — Federal Court erring in determination that standard of review regarding interpretative issue reasonableness not correctness — Interpretation of phrase "arose out of or was directly connected with" in Act, s. 21(2)(a) discrete question of law in dispute before Board capable of being considered separately — Determination by Federal Court of Appeal in Frye v. Canada (Attorney General) that correctness standard must be used in considering interpretation of phrase "arose out of or was directly connected with" in

A-226-14
2015 CAF 119

Anne Cole (*appelante*)

c.

Procureur général du Canada (*intimé*)

Répertorié : Cole c. Canada

Cour d'appel fédérale, juges Gauthier, Ryer et Webb, J.C.A.—Ottawa, 25 février et 5 mai 2015.

Anciens combattants — Appel d'une décision par laquelle la Cour fédérale a rejeté la demande de contrôle judiciaire d'une décision du Tribunal des anciens combattants rejetant la demande de pension d'invalidité relative à une affection alléguée de dépression majeure présentée par l'appelante, conformément à l'art. 21(2)a) de la Loi sur les pensions — La carrière militaire de l'appelante a pris fin lorsqu'elle fut libérée pour raisons médicales parce qu'elle souffrait de quatre affections, dont une dépression majeure — L'appelante a déposé une demande auprès du ministère des Anciens Combattants (le MAC) en vue d'obtenir une pension d'invalidité en ce qui concernait son service militaire — Conformément à l'art. 21(2)a), le demandeur doit établir un lien de causalité entre l'affection alléguée et son service militaire pour avoir droit à une pension d'invalidité — Le dossier dont disposait le Tribunal comportait des éléments de preuve selon lesquels la dépression de l'appelante pouvait être rattachée à des facteurs découlant de son service militaire (facteurs militaires) et à des facteurs découlant de sa vie personnelle (facteurs personnels) — Le Tribunal a rejeté la demande de pension d'invalidité de l'appelante puisqu'elle n'avait pas établi que les facteurs militaires avaient causé ou aggravé son affection allégué — La Cour fédérale a jugé que l'appréciation des éléments de preuve par le Tribunal et l'interprétation qu'il a faite de sa loi habilitante étaient assujetties à la norme de la décision raisonnable — Elle a conclu que le Tribunal avait interprété l'expression « consécutive à » à l'art. 21(2)a) de la Loi sur les pensions comme exigeant que le service militaire de l'appelante soit la « cause principale ou majeure » de sa dépression, puis a conclu qu'en retenant cette interprétation, le Tribunal n'a commis aucune erreur susceptible de contrôle — Il s'agissait de savoir si la Cour fédérale a commis une erreur lorsqu'elle a conclu que la norme de contrôle applicable à la question d'interprétation était la norme de la décision raisonnable; quelle est l'interprétation correcte de l'exigence de causalité correspondant aux mots « rattachée directement [à] » à l'art. 21(2)a) de la Loi sur les pensions; et si l'interprétation des mots « rattachée directement [à] » à l'art. 21(2)a) de la Loi comme exigeant une causalité

Act, s. 21(2)(a) satisfactory determination of applicability of correctness standard to interpretation of those words in Act, s. 21(2)(a) as required herein — For number of reasons, present case constituting one of cases in which standard of correctness properly applicable on interpretation of tribunal's home statute — As to Board's interpretation of causal connection requirement, record showing that both military, personal factors of appellant having direct causal connection with appellant's claimed condition — However, appellant not required to establish that military factors playing larger role in triggering major depression than personal factors — Board's primary cause interpretation of causal connection requirement in phrase "directly connected with" incorrect — Court specifically instructed by Act, s. 2, Veterans Review and Appeal Board Act (VRAB Act), s. 3 on how Board, any reviewing court must interpret Act's provisions — Federal Court's adoption of ordinary civil standard of causation in this case inconsistent with parliamentary admonishments in Act, s. 2, VRAB Act, s. 3 — For purposes of establishing entitlement to disability pension under Act, s. 21(2)(a) on basis claimed condition "directly connected with" applicant's military service, applicant must establish only significant causal connection between applicant's claimed condition, military service — Board's primary cause interpretation of causal connection requirement in phrase "directly connected with" in Act, s. 21(2)(a) also unreasonable — Parliament mandating that liberal interpretation of Act must be given to ensure our country's obligation to members of armed forces who have been disabled or have died from military service fulfilled — Lower level of causal connection than ordinary civil standard of "but for" test intended by Parliament — Per Gauthier J.A. (concurring reasons): Regarding standard of review in this case, correctness not standard to be applied to Board's interpretation of Act, s. 21(2)(a) but rather reasonableness given recent Supreme Court of Canada case law — Appeal allowed.

correspondant au critère de la cause principale était raisonnable — La Cour fédérale a commis une erreur lorsqu'elle a conclu que la norme de contrôle applicable relativement à la question d'interprétation était celle de la décision raisonnable et non celle de la décision correcte — L'interprétation des mots « consécutive ou rattachée directement [à] » à l'art. 21(2)a) de la Loi est une question de droit qui était controversée devant le Tribunal et il s'agissait d'une question de droit distincte susceptible d'être examinée séparément — L'enseignement de la Cour d'appel fédérale par la jurisprudence Frye c. Canada (Procureur général) selon lequel il faut appliquer la norme de la décision correcte lors de l'examen de l'interprétation des mots « consécutive ou rattachée directement [à] » à l'art. 21(2)a) de la Loi peut être considéré comme une conclusion saine quant à l'applicabilité de la norme de la décision correcte à l'interprétation de ces mêmes mots à l'art. 21(2)a), soit la mission qui incombe à la Cour dans le présent appel — Il peut y avoir des cas où la norme de la décision correcte est appliquée à juste titre relativement à l'interprétation de la « loi constitutive » d'un tribunal administratif et, pour de nombreuses raisons, tel est le cas en l'espèce — En ce qui concerne l'interprétation du Tribunal de l'exigence d'un lien de causalité, il ressort du dossier que les facteurs militaires et les facteurs personnels avaient une causalité directe avec l'affection alléguée de l'appelante — Toutefois, l'appelante n'était pas tenue d'établir que les facteurs militaires avaient joué un rôle plus important que les facteurs personnels dans le développement de sa dépression majeure — L'interprétation par le Tribunal de l'exigence de causalité correspondant aux mots « rattachée directement [à] » qui conduit au critère de la cause principale était incorrecte — Des instructions précises étaient données à la Cour par l'art. 2 de la Loi et par l'art. 3 de la Loi sur le Tribunal des anciens combattants (révision et appel) (Loi sur le TACRA), sur la manière dont le Tribunal et toute cour réformatrice doivent interpréter les dispositions de la Loi sur les pensions — L'adoption par la Cour fédérale de cette norme civile ordinaire était incompatible avec les directives que le législateur a donné à l'art. 2 de la Loi sur les pensions et à l'art. 3 de la Loi sur le TACRA — Pour établir le droit à une pension d'invalidité en vertu de l'art. 21(2)a) de la Loi au motif que l'affection alléguée était « rattachée directement au » service militaire du demandeur, le demandeur doit seulement établir une causalité importante entre son affection alléguée et son service militaire — L'interprétation par le Tribunal des mots « rattachée directement [à] » à l'art. 21(2)a) de la Loi comme exigeant une causalité correspondant au critère de la cause principale était aussi déraisonnable — Le législateur exige que la Loi soit interprétée de façon libérale, afin d'assurer que notre pays honore ses obligations envers les membres des forces armées qui sont devenus invalides ou sont décédés par suite de leur service militaire — Il s'ensuit que le législateur envisageait un degré de causalité inférieur à celui de la norme civile ordinaire du critère du facteur déterminant — La juge Gauthier, J.C.A. (motifs concourants) : Pour ce qui concerne la norme de

contrôle, la norme de la décision correcte n'était pas la norme applicable à l'interprétation du Tribunal de l'art. 21(2)a) de la Loi, mais plutôt celle de la raisonnabilité, étant donné la jurisprudence de la Cour suprême du Canada — Appel accueilli.

This was an appeal from a Federal Court decision dismissing the appellant's application for judicial review. The decision under review was made by the Veterans Review and Appeal Board, pursuant to section 29 of the *Veterans Review and Appeal Board Act* (VRAB Act), wherein the Board refused to grant the appellant's application for a disability pension pursuant to paragraph 21(2)(*a*) of the *Pension Act* for the claimed condition of major depression. The appellant's military career ended when she was medically discharged on account of four conditions, including major depression and chronic dysthymia with obsessive compulsive traits. She then applied to the Department of Veterans Affairs (DVA) for a disability pension in respect of her military service on account of her major depression. The DVA considered that her application was brought under paragraph 21(2)(*a*) of the Act. Under paragraph 21(2)(*a*) of the Act, a disability pension in respect of peace time military service cannot be granted unless the applicant's injury or disease (the claimed condition), or an aggravation thereof, "arose out of or was directly connected" with the applicant's military service. This language requires the applicant to establish a causal connection between the claimed condition and his or her military service. The record before the Board contained evidence that the appellant's depression could be traced to factors relating to her military service (military factors) and factors relating to her personal life (personal factors). The Board rejected the appellant's application for a disability pension on the basis that she failed to establish that the military factors caused or aggravated her claimed condition. The appellant's military factors included a number of work-related stressors and disappointments. As to the personal factors, in particular, the appellant's spouse, another member of the military, was required to be away, causing her stress as she cared for the children of the marriage without assistance from her husband.

Il s'agissant d'un appel visant une décision de la Cour fédérale rejetant la demande de contrôle judiciaire présentée par l'appelante. La décision attaquée avait été rendue par le Tribunal des anciens combattants en vertu de l'article 29 de la *Loi sur le Tribunal des anciens combattants (révision et appel)* (la Loi sur le TACRA). Aux termes de cette décision, le Tribunal avait rejeté la demande de pension d'invalidité relative à une affection alléguée de dépression majeure présentée par l'appelante, conformément à l'alinéa 21(2)*a*) de la *Loi sur les pensions*. La carrière militaire de l'appelante a pris fin lorsqu'elle fut libérée pour raisons médicales parce qu'elle souffrait de quatre affections, dont une dépression majeure et une dysthymie chronique à caractère obsessionnel compulsif. L'appelante a ensuite déposé une demande auprès du ministère des Anciens Combattants (le MAC) en vue d'obtenir une pension d'invalidité en ce qui concernait son service militaire fondée sur sa dépression majeure. Le MAC a conclu que sa demande était faite en vertu de l'alinéa 21(2)*a*) de la Loi. Une pension d'invalidité en ce qui concerne le service militaire en temps de paix ne peut être accordée sous le régime de l'alinéa 21(2)*a*) de la Loi, à moins que la blessure ou la maladie du demandeur (l'affection alléguée) — ou son aggravation — soit « consécutive ou rattachée directement » au service militaire du demandeur. Ce texte exige que le demandeur établisse un lien de causalité entre l'affection alléguée et son service militaire. Le dossier dont disposait le Tribunal comportait des éléments de preuve selon lesquels la dépression de l'appelante pouvait être rattachée à des facteurs découlant de son service militaire (facteurs militaires) et à des facteurs découlant de sa vie personnelle (facteurs personnels). Le Tribunal a rejeté la demande de pension d'invalidité de l'appelante, au motif qu'elle n'avait pas réussi à établir que les facteurs militaires avaient causé ou aggravé son affection alléguée. Les facteurs militaires de l'appelante comprenaient plusieurs facteurs de stress et de déceptions découlant du travail. Quant aux facteurs personnels, l'époux de l'appelante, un militaire lui aussi, a dû séjourner à l'extérieur et ces absences étaient une source de stress pour l'appelante parce qu'elle devait s'occuper seule des enfants du mariage.

The Federal Court determined that the Board's weighing of the evidence and interpretation of the statutory scheme was reviewable on the standard of reasonableness. It determined that the Board required the appellant to establish that the military factors were the "primary cause" of the claimed condition. It dismissed the appellant's review application on the basis that the evidence before the Board was sufficient to support its conclusion that the appellant's medical condition was not caused by her military service. It concluded that the

La Cour fédérale a confirmé que l'appréciation des éléments de preuve par le Tribunal et l'interprétation qu'il a faite de sa loi habilitante étaient assujetties à la norme de la décision raisonnable. Elle a conclu que le comité avait exigé que l'appelante établisse que les facteurs militaires étaient la « cause principale » de l'affection alléguée. La Cour a rejeté la demande au motif que les éléments de preuve dont disposait le Tribunal allaient dans le sens de sa conclusion selon laquelle l'affection médicale de l'appelante ne découlait pas

Board interpreted "arose out of" in paragraph 21(2)(*a*) of the *Pension Act* as requiring the appellant's military service to be the "primary or major cause" of her depression and then found that the Board made no reviewable error in using that interpretation.

The issues were whether the Federal Court erred in selecting reasonableness as the standard of review regarding the interpretative issue; if correctness was the required standard of review with respect to the interpretative issue, what was the correct interpretation of the causal connection requirement of the phrase "arose out of or was directly connected with" in paragraph 21(2)(*a*) of the *Pension Act*; and whether the Board's primary cause interpretation of the causal connection requirement of the phrase "arose out of or was directly connected with" in paragraph 21(2)(*a*) of the Act was unreasonable.

Held, the appeal should be allowed.

Subsection 21(2) of the Act applies in respect of service in the militia or reserve army in peace time. The connectivity language in subsection 21(2) regarding injury, disease or death of a serviceman or woman and his or her peacetime military service is "arose out of or was directly connected with" such military service. This phrase requires a higher degree of causal connection between the death, injury or disease and the peacetime military service than is required by the phrase "attributable to or incurred during" in subsection 21(1) of the Act, which deals with services rendered during war or special duty service. The Federal Court concluded that the issue before the Board was one of mixed fact and law (interpretation of the Act and the application thereof to the facts), which typically attracts review on the standard of reasonableness. The interpretation of the phrase "arose out of or was directly connected with" in paragraph 21(2)(*a*) of the Act was a question of law that was in dispute before the Board. It was a discrete question of law capable of being considered separately. However, in reviewing the Board's interpretation of this phrase, the Federal Court applied the reasonableness standard, not the correctness standard. The determination by the Federal Court of Appeal in *Frye v. Canada (Attorney General)* that the correctness standard must be used in considering the interpretation of the phrase "arose out of or was directly connected with" in paragraph 21(2)(*a*) of the Act was regarded as a satisfactory determination of the applicability of the correctness standard to the interpretation of those exact words in paragraph 21(2)(*a*) as required in this appeal. Moreover, the discernment of the standard of causation that was intended by Parliament when it enacted the phrase "arose out of or was directly connected with" in paragraph 21(2)(*a*) of the Act is a question of importance that extends beyond the ambit of the Act. Also, discerning degrees of causal connection is not a matter with which the Board would regularly

de son service militaire. Elle a conclu que le Tribunal avait interprété l'expression « consécutive à » à l'alinéa 21(2)*a*) de la *Loi sur les pensions* comme exigeant que le service militaire de l'appelante soit la « cause principale ou majeure » de sa dépression, puis a conclu qu'en retenant cette interprétation, le Tribunal n'a commis aucune erreur susceptible de contrôle.

Il s'agissait de savoir si la Cour fédérale a commis une erreur lorsqu'elle a conclu que la norme de contrôle applicable à la question d'interprétation était la norme de la décision raisonnable; si la norme de contrôle applicable à la question d'interprétation est la norme de la décision correcte, quelle est l'interprétation correcte de l'exigence de causalité correspondant aux mots « rattachée directement [à] » à l'alinéa 21(2)*a*) de la *Loi sur les pensions*; et si l'interprétation des mots « rattachée directement [à] » à l'alinéa 21(2)*a*) de la Loi comme exigeant une causalité correspondant au critère de la cause principale était raisonnable.

Arrêt : l'appel doit être accueilli.

Le paragraphe 21(2) de la Loi s'applique relativement au service dans la milice ou dans l'armée de réserve en temps de paix. Le lien entre la blessure, la maladie ou le décès d'un militaire et son service militaire en temps de paix est évoqué par l'expression « consécutive ou rattachée directement [à] » ce service militaire. Ces mots exigent un degré plus élevé de causalité entre, d'une part, le décès, la blessure ou la maladie, et d'autre part, le service militaire en temps de paix, que ce qu'exigent les mots « survenue au cours […] ou attribuable à » au paragraphe 21(1) de la Loi, qui porte sur le service en temps de guerre ou le service spécial. La Cour fédérale a conclu que la question dont le Tribunal avait été saisi était une question mélangée de fait et de droit (interprétation de la Loi et application des faits), qui commande généralement un examen selon la norme de la raisonnabilité. L'interprétation des mots « consécutive ou rattachée directement [à] » à l'alinéa 21(2)*a*) de la Loi est une question de droit qui était controversée devant le Tribunal. Il s'agissait d'une question de droit distincte susceptible d'être examinée séparément. Toutefois, la Cour fédérale a appliqué la norme de la décision raisonnable, et non celle de la décision correcte, dans le cadre de son examen de l'interprétation que le Tribunal avait faite de ces mots. L'enseignement de la Cour d'appel fédérale par la jurisprudence *Frye c. Canada (Procureur général)* selon lequel il faut appliquer la norme de la décision correcte lors de l'examen de l'interprétation des mots « consécutive ou rattachée directement [à] » à l'alinéa 21(2)*a*) de la Loi pouvait être considéré comme une conclusion saine quant à l'applicabilité de la norme de la décision correcte à l'interprétation de ces mêmes mots à l'alinéa 21(2)*a*), soit la mission qui incombe à la Cour dans le présent appel. En outre, la détermination de la norme de causalité que le législateur a voulu établir en promulguant les mots « consécutive ou rattachée directement [à] » à l'alinéa 21(2)*a*) de la Loi est une

grapple, a task that courts are better suited to perform. For a number of reasons, this was one of those cases in which the standard of correctness was properly applicable with respect to the interpretation of the home statute of a tribunal. Therefore, the Federal Court erred in its determination that the standard of review regarding the interpretative issue was reasonableness and not correctness.

The Board interpreted the phrase at issue in paragraph 21(2)(*a*) as requiring an applicant for a disability pension to establish that his or her military service was the primary cause of his or her claimed condition. There is disagreement at the Federal Court level as to whether the primary cause level of causal connection is required by the phrase "arose out of or was directly connected with". Based on the decision in *Frye*, the causal connection requirements in the phrase "arose out of" can be satisfied in two ways: by either a direct causal connection or a non-direct causal connection. In this case, the record showed that both the military factors and the personal factors had a direct causal connection with the appellant's claimed condition. Where the claimed condition is traceable to two direct causes, the interpretative issue is whether the phrase "directly connected with" requires the applicant to establish that his or her military service is the primary cause of that condition. Here, it had to be determined whether the appellant was required to establish that the military factors played a larger role in bringing about her major depression than the personal factors. The primary cause interpretation of the causal connection requirement in the phrase "directly connected with" was incorrect. A textual, contextual and purposive analysis were conducted for interpretative reasons. It could be reasonably concluded that contextually considered, the phrase "directly connected with" was intended to require a higher degree of causal connection between the claimed condition and peacetime military service than that required under subsection 21(1) of the Act. However, that contextual comparison did not establish that the primary cause level of causation was necessarily mandated. Purposively considered, in these circumstances, the Court was specifically instructed by section 2 of the Act and section 3 of the VRAB Act on how the Board and any reviewing court must interpret the Act's provisions. While the Federal Court's adoption of the ordinary civil standard of causation in this case was consistent with the level of factual causation commonly applied in tort cases, it was inconsistent with the parliamentary admonishments in section 2 of the Act and section 3 of the VRAB Act. A lower level of causal connection than the "but for" test was required by the phrase "directly connected with" in paragraph 21(2)(*a*) of the Act. Otherwise, the liberal interpretative admonishments would have no meaning in the circumstances under consideration. Thus, an

question d'importance qui déborde le cadre de la Loi. De plus, le Tribunal n'est pas régulièrement appelé à discerner des degrés de causalité, le juge judiciaire étant mieux à même de remplir cette mission. Il peut y avoir des cas où la norme de la décision correcte est appliquée à juste titre relativement à l'interprétation de la « loi constitutive » d'un tribunal administratif et, pour de nombreuses raisons, tel était le cas en l'espèce. En conséquence, la Cour fédérale a commis une erreur lorsqu'elle a conclu que la norme de contrôle applicable relativement à la question d'interprétation était celle de la décision raisonnable et non celle de la décision correcte.

Le Tribunal a interprété ces mots comme exigeant que l'auteur de la demande de pension d'invalidité faite en vertu de l'alinéa 21(2)*a*) établisse que son service militaire avait été la cause principale de son affection alléguée. Il y a désaccord au sein de la Cour fédérale quant à savoir si les mots « consécutive ou rattachée directement [à] » exigent un degré de causalité correspondant au critère de la « cause principale ». La jurisprudence *Frye* enseigne qu'il y a deux types de causalité qui peuvent satisfaire aux exigences de causalité correspondant aux mots « consécuti[ve] ou rattaché[e] directement à » : la causalité directe ou la causalité indirecte. Dans la présente affaire, il ressort du dossier que les facteurs militaires et les facteurs personnels avaient une causalité directe avec l'affection alléguée de l'appelante. Lorsque l'affection alléguée peut être rattachée à deux causes directes, la question d'interprétation est celle de savoir si les mots « rattachée directement [à] » exigent que le demandeur établisse que son service militaire est la cause principale de cette affection. En l'espèce, la question qui se posait était celle de savoir si l'appelante devait établir que les facteurs militaires avaient joué un rôle plus important que les facteurs personnels dans le développement de sa dépression majeure. L'interprétation de l'exigence de causalité correspondant aux mots « rattachée directement [à] » qui conduit au critère de la cause principale était incorrecte. Un examen textuel, contextuel et téléologique a été effectué pour des raisons d'interprétation. On pourrait raisonnablement conclure que, d'après l'examen contextuel, les mots « rattachée directement [à] » étaient censés exiger un degré plus élevé de causalité entre l'affection alléguée et le service militaire en temps de paix que ce qu'exige le paragraphe 21(1) de la Loi. Toutefois, cette comparaison contextuelle n'a pas établi que le niveau de causalité requis est nécessairement celui de la cause principale. Dans l'ensemble, des instructions précises étaient données à la Cour par l'article 2 de la Loi et par l'article 3 de la Loi sur le TACRA, sur la manière dont le Tribunal et toute cour réformatrice doivent interpréter les dispositions de la *Loi sur les pensions*. Bien que l'adoption par la Cour de cette norme civile ordinaire corresponde en l'espèce au degré de causalité qui est généralement appliqué dans les affaires de responsabilité civile délictuelle, elle était incompatible avec les directives que le législateur nous donne à l'article 2 de la Loi et à l'article 3 de la Loi sur le TACRA. Les mots « rattachée directement [à] » à

interpretation of the phrase "directly connected with" that requires that a pension applicant's military service was the primary cause of his or her claimed condition was incorrect.

As to the degree of causation that is required to establish a direct causal connection, for the purposes of establishing entitlement to a disability pension under paragraph 21(2)(*a*) of the Act on the basis that the claimed condition was "directly connected with" the applicant's military service, the applicant must establish only a significant causal connection between the applicant's claimed condition and his or her military service. In other words, a causal connection that is significant but less than primary will be sufficient. Thus, an applicant's military service will provide a sufficient causal connection with his or her claimed condition such that the claimed condition is "directly connected with" such military service where he or she establishes that his or her military service was a significant factor in bringing about that claimed condition.

The Board's primary cause interpretation of the causal connection requirement in the phrase "directly connected with" in paragraph 21(2)(*a*) was also unreasonable. Parliament has mandated that a liberal interpretation of the Act must be given to ensure that our country's obligation to members of the armed forces who have been disabled or have died as a result of military service may be fulfilled. This means that a lower level of causal connection than the ordinary civil standard of the "but for" test was intended by Parliament when it enacted the phrase "directly connected with". Thus, in adhering to the primary cause level of causation, the Board unreasonably interpreted the phrase "directly connected with". The significant-cause level of causation provides a flexible approach to the establishment of the requisite causal connection between military service and a claimed condition and is fully consistent with the liberal interpretation admonishments contained in section 2 of the Act and section 3 of the VRAB Act. This flexibility favourably distinguishes the significant cause interpretation from the primary cause interpretation. Therefore, an interpretation of the phrase "directly connected with" in paragraph 21(2)(*a*) of the Act that requires an applicant to establish that his or her military service is the primary cause of his or her claimed condition is unreasonable and a decision to deny the award on the basis of such an interpretation was not within the range of reasonable outcomes of the decision-making process under consideration.

l'alinéa 21(2)*a*) de la Loi exigeaient un degré de causalité inférieur à celui du critère du facteur déterminant. Autrement, l'appel à une interprétation libérale n'aurait aucun sens dans les circonstances de l'espèce. Par conséquent, une interprétation des mots « rattachée directement [à] » qui exige que le service militaire d'un demandeur de pension ait été la cause principale de son affection alléguée était incorrecte.

En ce qui concerne le degré de causalité exigé pour établir une causalité directe, pour établir le droit à une pension d'invalidité en vertu de l'alinéa 21(2)*a*) de la Loi au motif que l'affection alléguée était « rattachée directement au » service militaire du demandeur, le demandeur doit seulement établir une causalité importante entre son affection alléguée et son service militaire. Autrement dit, une causalité qui est importante, mais moins que principale, sera suffisante. Ainsi, le service militaire du demandeur présentera une causalité suffisante avec son affection alléguée pour que l'on puisse considérer que celle-ci est « rattachée directement [à] » ce service militaire lorsque le demandeur établit que son service militaire a été un facteur important dans le déclenchement de l'affection alléguée.

L'interprétation par le Tribunal des mots « rattachée directement [à] » à l'alinéa 21(2)*a*) comme exigeant une causalité correspondant au critère de la cause principale était aussi déraisonnable. Le législateur exige que la Loi soit interprétée de façon libérale, afin d'assurer que notre pays honore ses obligations envers les membres des forces armées qui sont devenus invalides ou sont décédés par suite de leur service militaire. Il s'ensuit que le législateur envisageait un degré de causalité inférieur à celui de la norme civile ordinaire du critère du facteur déterminant lorsqu'il a promulgué les mots « rattachée directement [à] ». Ainsi, en retenant le degré de causalité correspondant au critère de la cause principale, le Tribunal a interprété de manière déraisonnable les mots « rattachée directement [à] ». Le degré de causalité de la cause importante permet une approche souple à l'égard de l'établissement de la causalité requise entre le service militaire et une affection alléguée et s'accorde parfaitement avec les exigences d'une interprétation libérale énoncées à l'article 2 de la Loi et à l'article 3 de la Loi sur le TACRA. Cette souplesse démarque favorablement l'interprétation conduisant au critère de la cause importante de l'interprétation conduisant au critère de la cause principale. En conséquence, l'interprétation des mots « rattachée directement [à] » à l'alinéa 21(2)*a*) de la Loi qui exige qu'un demandeur établisse que son service militaire est la cause principale de son affection alléguée est déraisonnable, ainsi qu'une décision de refuser une pension sur le fondement d'une telle interprétation, n'appartenaient pas aux issues raisonnables possibles du processus décisionnel en cause.

Since it was concluded that the Board erred in its selection of the primary cause test to determine whether the appellant's claimed condition was sufficiently causally connected to her military service, clearly the Board's decision to deny her application for a disability pension could not stand.

Per Gauthier J.A. (concurring reasons): With respect to the standard of review, correctness was not the standard to be applied to the Board's interpretation of paragraph 21(2)(*a*) of the Act. The Supreme Court has stated that reasonableness is the presumptive standard of review where a tribunal is interpreting its home statute or a statute closely related to its function. In view of case law subsequent to *Frye v. Canada (Attorney General)*, the presumption of reasonableness was not rebutted in this case. The interpretation offered by Ryer J.A. ensured that the scheme of the Act was not rendered meaningless: insignificant service-related factors cannot be sufficient to trigger the compensation scheme. On the other hand, allowing the mechanism provided by paragraph 21(2)(*a*) when the service-related factors are significant to be triggered gives effect to Parliament's clear intention that this benefits scheme be liberally construed to ensure that this country's obligation towards members of the armed forces is met.

Puisqu'il a été conclu que le Tribunal avait commis une erreur dans le choix du critère de la cause principale pour établir s'il y avait un lien de causalité suffisant entre l'affection alléguée de l'appelante et son service militaire, il est clair que la décision du Tribunal de refuser sa demande de pension d'invalidité ne pouvait être confirmée.

La juge Gauthier, J.C.A. (motifs concourants) : Pour ce qui concerne la norme de contrôle, la norme de la décision correcte n'était pas la norme applicable à l'interprétation que le Tribunal a faite de l'alinéa 21(2)*a*) de la Loi. La Cour suprême enseigne que la norme de la raisonnabilité est présumée jouer lorsqu'un tribunal interprète sa loi constitutive ou une loi étroitement reliée à sa mission. Compte tenu de la jurisprudence subséquente à l'arrêt *Frye c. Canada (Procureur général)*, la présomption d'assujettissement à la norme de la décision raisonnable n'a pas été réfutée en l'espèce. L'interprétation proposée par le juge Ryer assurait que le régime de la Loi n'était pas vide de sens : les facteurs négligeables reliés au service ne peuvent pas être considérés comme suffisants pour donner droit à une pension au titre du régime. En revanche, permettre au demandeur de se prévaloir du mécanisme prévu à l'alinéa 21(2)*a*) lorsque les facteurs reliés au service sont importants donne effet à l'intention claire du législateur selon laquelle ce régime de prestations s'interprète de façon libérale, de manière à assurer que l'obligation de ce pays envers les membres des forces armées est remplie.

STATUTES AND REGULATIONS CITED

Canada Labour Code, R.S.C., 1985, c. L-2.
Pension Act, R.S.C., 1985, c. P-6, ss. 2, 3 "disability", 21(1),(2).
Veterans Review and Appeal Board Act, S.C. 1995, c. 18, ss. 3, 29.

LOIS ET RÈGLEMENTS CITÉS

Code canadien du travail, L.R.C. (1985), ch. L-2.
Loi sur le Tribunal des anciens combattants (révision et appel), L.C. 1995, ch. 18, art. 3, 29.
Loi sur les pensions, L.R.C. (1985), ch. P-6, art. 2, 3 « invalidité », 21(1),(2).

CASES CITED

APPLIED:

Dunsmuir v. New Brunswick, 2008 SCC 9, [2008] 1 S.C.R. 190; *Frye v. Canada (Attorney General)*, 2005 FCA 264, 338 N.R. 382 (as to standard of review); *Atomic Energy of Canada Ltd. v. Wilson*, 2015 FCA 17, [2015] 4 F.C.R. 468; *McLean v. British Columbia (Securities Commission)*, 2013 SCC 67, [2013] 3 S.C.R. 895; *Mathew v. Canada*, 2005 SCC 55, [2005] 2 S.C.R. 643.

DISTINGUISHED:

Frye v. Canada (Attorney General), 2005 FCA 264, 338 N.R. 382.

JURISPRUDENCE CITÉE

DÉCISIONS APPLIQUÉES :

Dunsmuir c. Nouveau-Brunswick, 2008 CSC 9, [2008] 1 R.C.S. 190; *Frye c. Canada (Procureur général)*, 2005 CAF 264 (quant à la norme de contrôle judiciaire); *Énergie atomique du Canada limitée c. Wilson*, 2015 CAF 17, [2015] 4 R.C.F. 468; *McLean c. Colombie-Britannique (Securities Commission)*, 2013 CSC 67, [2013] 3 R.C.S. 895; *Mathew c. Canada*, 2005 CSC 55, [2005] 2 R.C.S. 643.

DÉCISION DIFFÉRENCIÉE :

Frye c. Canada (Procureur général), 2005 CAF 264.

CONSIDERED:

Agraira v. Canada (Public Safety and Emergency Preparedness), 2013 SCC 36, [2013] 2 S.C.R. 559; *Attaran v. Canada (Attorney General)*, 2015 FCA 37, 380 D.L.R. (4th) 737; *Canadian Artists' Representation v. National Gallery of Canada*, 2014 SCC 42, [2014] 2 S.C.R. 197.

REFERRED TO:

John Doe v. Canada (Attorney General), 2004 FC 451, 249 F.T.R. 301; *Boisvert v. Canada (Attorney General)*, 2009 FC 735; *Hall v. Canada (Attorney General)*, 2011 FC 1431.

AUTHORS CITED

Canada. Parliament. *House of Commons Debates*, 19th Parl., 2nd Sess., Vol. III (May 27, 1941) (Hon. W. L. MacKenzie King).

APPEAL from a Federal Court decision (2014 FC 310) dismissing the appellant's application for judicial review of a Veterans Review and Appeal Board decision refusing to grant the appellant's application for a disability pension pursuant to paragraph 21(2)(*a*) of the *Pension Act* for the claimed condition of major depression. Appeal allowed.

APPEARANCES

Stephen B. Acker and *Yael Wexler* for appellant.
Craig Collins-Williams for respondent.

SOLICITORS OF RECORD

Faskin Martineau DuMoulin LLP, Ottawa, for appellant.
Deputy Attorney General of Canada for respondent.

The following are the reasons for judgment rendered in English by

[1] RYER J.A.: This is an appeal from a decision (2014 FC 310) of Mr. Justice de Montigny of the Federal Court (the Federal Court Judge) in which he dismissed an application for judicial review brought by Anne Cole. The decision under review was made by the Veterans Review and Appeal Board (the Board), pursuant to

DÉCISIONS EXAMINÉES :

Agraira c. Canada (Sécurité publique et Protection civile), 2013 CSC 36, [2013] 2 R.C.S. 559; *Attaran c. Canada (Procureur général)*, 2015 CAF 37; *Front des artistes canadiens c. Musée des beaux-arts du Canada*, 2014 CSC 42, [2014] 2 R.C.S. 197.

DÉCISIONS CITÉES :

John Doe c. Canada (Procureur général), 2004 CF 451; *Boisvert c. Canada (Procureur général)*, 2009 CF 735; *Hall c. Canada (Procureur général)*, 2011 CF 1431.

DOCTRINE CITÉE

Canada. Parlement. *Débats de la Chambre des communes*, 19e lég., 2e sess., vol. III (27 mai 1941) (L'hon. W. L. MacKenzie King).

APPEL d'une décision de la Cour fédérale (2014 CF 310) rejetant la demande de contrôle judiciaire présentée par l'appelante visant une décision du Tribunal des anciens combattants de rejeter sa demande de pension d'invalidité relative à une affection alléguée de dépression majeure conformément à l'alinéa 21(2)*a*) de la *Loi sur les pensions*. Appel accueilli.

ONT COMPARU

Stephen B. Acker et *Yael Wexler* pour l'appelante.
Craig Collins-Williams pour l'intimé.

AVOCATS INSCRITS AU DOSSIER

Faskin Martineau DuMoulin S.E.N.C.R.L., s.r.l., Ottawa, pour l'appelante.
Le sous-procureur général du Canada pour l'intimé.

Ce qui suit est la version française des motifs du jugement rendus par

[1] LE JUGE RYER, J.C.A. : Notre Cour est saisie d'un appel visant une décision (2014 CF 310) rendue par le juge de Montigny de la Cour fédérale (le juge de la Cour fédérale), par laquelle celui-ci a rejeté la demande de contrôle judiciaire présentée par Mme Anne Cole (Mme Cole). La décision attaquée avait été rendue par

section 29 of the *Veterans Review and Appeal Board Act*, S.C. 1995, c. 18 (the VRAB Act), on September 10, 2012. In it, the Board refused to grant Ms. Cole's application for a disability pension, pursuant to paragraph 21(2)(*a*) of the *Pension Act*, R.S.C., 1985, c. P-6 (the *Pension Act*), for the claimed condition of major depression.

[2] Captain Cole's 21-year military career ended on February 1, 2007, when she was medically discharged on account of four conditions, including major depression and chronic dysthymia with obsessive compulsive traits.

[3] After her discharge, Ms. Cole made an application to the Department of Veterans Affairs (the DVA) for a disability pension in respect of her military service on account of her major depression. The DVA considered that her application was brought under paragraph 21(2)(*a*) of the *Pension Act*, which reads as follows:

21. …

Service in militia or reserve army and in peace time

(2) In respect of military service rendered in the non-permanent active militia or in the reserve army during World War II and in respect of military service in peace time,

(*a*) where a member of the forces suffers disability resulting from an injury or disease or an aggravation thereof that arose out of or was directly connected with such military service, a pension shall, on application, be awarded to or in respect of the member in accordance with the rates for basic and additional pension set out in Schedule I;

[4] A disability pension in respect of peace time military service cannot be granted under paragraph 21(2)(*a*) of the *Pension Act* unless the applicant's injury or disease (the claimed condition), or an aggravation thereof, "arose out of or was directly connected" with the applicant's military service. This language requires the applicant to

le Tribunal des anciens combattants (révision et appel) (le Tribunal), en vertu de l'article 29 de la *Loi sur le Tribunal des anciens combattants (révision et appel)*, L.C. 1995, ch. 18 (la Loi sur le TACRA), le 10 septembre 2012. Aux termes de cette décision, le Tribunal avait rejeté la demande de pension d'invalidité relative à une affection alléguée de dépression majeure présentée par M^me^ Cole, conformément à l'alinéa 21(2)*a*) de la *Loi sur les pensions*, L.R.C. (1985), ch. P-6 (la *Loi sur les pensions*).

[2] La carrière militaire de 21 ans de la capitaine Cole a pris fin le 1^er^ février 2007, lorsqu'elle fut libérée pour raisons médicales parce qu'elle souffrait de quatre affections, dont une dépression majeure et une dysthymie chronique à caractère obsessionnel compulsif.

[3] Après sa libération, M^me^ Cole a déposé une demande auprès du ministère des Anciens Combattants (le MAC) en vue d'obtenir une pension d'invalidité en ce qui concernait son service militaire fondée sur sa dépression majeure. Le MAC a conclu que la demande de M^me^ Cole était faite en vertu de l'alinéa 21(2)*a*) de la *Loi sur les pensions*, qui est ainsi rédigé :

21. […]

Milice active non permanente ou armée de réserve en temps de paix

(2) En ce qui concerne le service militaire accompli dans la milice active non permanente ou dans l'armée de réserve pendant la Seconde Guerre mondiale ou le service militaire en temps de paix :

a) des pensions sont, sur demande, accordées aux membres des forces ou à leur égard, conformément aux taux prévus à l'annexe I pour les pensions de base ou supplémentaires, en cas d'invalidité causée par une blessure ou maladie — ou son aggravation — consécutive ou rattachée directement au service militaire;

[4] Une pension d'invalidité en ce qui concerne le service militaire en temps de paix ne peut être accordée sous le régime de l'alinéa 21(2)*a*) de la *Loi sur les pensions*, à moins que la blessure ou la maladie du demandeur (l'affection alléguée) — ou son aggravation — soit « consécutive ou rattachée directement » au service

establish a causal connection between the claimed condition and his or her military service.

[5] The record before the Board contained evidence that Ms. Cole's depression could be traced to factors related to her military service (military factors) and factors related to her personal life (personal factors).

[6] The Board rejected Ms. Cole's application for a disability pension on the basis that she failed to establish that the military factors caused or aggravated her claimed condition.

[7] In reviewing the Board's decision, the Federal Court Judge determined that the Board required Ms. Cole to establish that the military factors were the "primary cause" of the claimed condition. In upholding the Board's decision, he concluded that the Board made no reviewable error in using "primary cause" as the degree of causation required by the phrase "arose out of" in paragraph 21(2)(*a*) of the *Pension Act*.

[8] For the reasons that follow, I am of the view that both the Board and the Federal Court Judge erred in their interpretation of the degree of causal connection required by the phrase "arose out of or was directly connected with" in relation to Ms. Cole's pension application.

[9] Because Ms. Cole's claimed condition was directly linked to both the military factors and the personal factors, the determinative issue in this appeal is the degree or extent of causal connection that is required to establish that her claimed condition "was directly connected with" her military service.

[10] In my view, that causal connection requirement will be satisfied if the military factors are established to have been a significant cause of her claimed condition. This is a lesser degree of causation than primary cause.

militaire du demandeur. Ce texte exige que le demandeur établisse un lien de causalité entre l'affection alléguée et son service militaire.

[5] Le dossier dont disposait le Tribunal comportait des éléments de preuve selon lesquels la dépression de M^me^ Cole pouvait être rattachée à des facteurs découlant de son service militaire (facteurs militaires) et à des facteurs découlant de sa vie personnelle (facteurs personnels).

[6] Le Tribunal a rejeté la demande de pension d'invalidité de M^me^ Cole, au motif qu'elle n'avait pas réussi à établir que les facteurs militaires avaient causé ou aggravé son affection alléguée.

[7] Le juge de la Cour fédérale, qui a examiné la décision du Tribunal a conclu que celui-ci avait exigé que M^me^ Cole établisse que les facteurs militaires étaient la « cause principale » de l'affection alléguée. Le juge a confirmé la décision du Tribunal, en concluant que ce dernier n'avait commis aucune erreur susceptible de contrôle lorsqu'il avait utilisé le critère de la « cause principale » comme degré de causalité exigé par les mots « consécutive [à] » à l'alinéa 21(2)*a*) de la *Loi sur les pensions*.

[8] Par les motifs qui suivent, je suis d'avis que le Tribunal et le juge de la Cour fédérale ont tous deux commis une erreur dans leur interprétation du degré de causalité exigé par les mots « consécutive ou rattachée directement [à] » relativement à la demande de pension de M^me^ Cole.

[9] Étant donné que l'affection alléguée de M^me^ Cole était directement rattachée aux facteurs militaires et aux facteurs personnels, la question déterminante dans le présent appel est le degré ou l'étendue de causalité qui est requis pour établir que l'affection alléguée de M^me^ Cole était « rattachée directement [à] » son service militaire.

[10] À mon avis, il sera satisfait à cette exigence de causalité s'il est établi que les facteurs militaires ont été une cause importante de l'affection alléguée de M^me^ Cole. Il s'agit d'un degré de causalité moindre que celui de la cause principale.

[11] Because the Board failed to apply this lesser degree of causal connection in assessing whether Ms. Cole's claimed condition "was directly connected with" her military service, I would return this matter to the Board to make this determination using such lesser degree of causal connection.

[11] Étant donné que le Tribunal a omis d'appliquer ce degré moindre de causalité lorsqu'il a apprécié la question de savoir si l'affection alléguée de M^me^ Cole était « rattachée directement [à] » son service militaire, je renverrais la présente affaire au Tribunal pour que celui-ci rende une nouvelle décision en utilisant ce degré moins strict quant au lien de causalité.

BACKGROUND

[12] In light of my conclusion that the outcome of this appeal is primarily a matter of statutory interpretation, a detailed review of the facts is not warranted.

[13] At all times that are relevant to this appeal, Ms. Cole was married to another member of the military. On a number of occasions during her military career, her husband was required to be away. These absences caused stress to Ms. Cole as she cared for the children of the marriage without assistance from her husband.

[14] It is not disputed that at the time of her release, Ms. Cole was suffering from major depression, which was the basis of her application for a disability pension in 2007 (appeal book, page 32).

[15] It is equally undisputed that, at all levels of review of her application, up to and including the review by the Board, there was cogent evidence to the effect that Ms. Cole's depression was grounded in both the military factors and the personal factors.

[16] The military factors included a number of work-related stressors and disappointments. Three work-related events caused Ms. Cole particular disappointment; namely, the failure to obtain a deployment to the former Yugoslavia in the mid-1990s, a less than outstanding personnel evaluation report in 1999 and the revocation of her approval for deployment to Washington in March of 2000. In addition, she was stressed by having to resort to the grievance procedure to remove the 1999 personnel evaluation report from her file.

LES FAITS

[12] Étant donné que j'ai conclu que l'issue du présent appel tenait principalement à une question d'interprétation des lois, il n'est pas nécessaire de procéder à un examen détaillé des faits.

[13] À toutes les époques pertinentes en l'espèce, M^me^ Cole était mariée à un autre militaire. À plusieurs occasions au cours de sa carrière militaire, son époux a dû séjourner à l'extérieur. Ces absences étaient une source de stress pour M^me^ Cole, parce qu'elle devait s'occuper des enfants du mariage sans l'aide de son époux.

[14] Il est constant qu'au moment de sa libération, M^me^ Cole souffrait d'une dépression majeure, sur laquelle était fondée sa demande de pension d'invalidité en 2007 (dossier d'appel, à la page 32).

[15] Il est également constant qu'à tous les stades de la procédure d'examen de sa demande, jusqu'à l'intervention du Tribunal inclusivement, il y avait une preuve convaincante que la dépression de M^me^ Cole avait été causée par des facteurs militaires et par des facteurs personnels.

[16] Les facteurs militaires comprenaient plusieurs facteurs de stress et de déceptions découlant du travail. Trois incidents liés au travail avaient donné lieu à une déception particulière chez M^me^ Cole; à savoir, le défaut d'obtenir un déploiement en ex-Yougoslavie au milieu des années 1990, un rapport d'appréciation du personnel plutôt ordinaire en 1999, et la révocation de son approbation aux fins d'un déploiement à Washington en mars 2000. De plus, elle avait été stressée par le fait de devoir recourir à la procédure de règlement des griefs en vue de faire retirer de son dossier le rapport d'appréciation du personnel de 1999.

[17] The personal factors included a difficult childhood and personality traits. With regard to personality traits, the evidence indicated that Ms. Cole has difficulties coping with relatively minor disappointments, suffers from a dysthymic disorder and has a maladaptive personality, predisposing her to depression.

[17] Les facteurs personnels comprenaient une enfance difficile et des traits de personnalité. Pour ce qui concerne les traits de personnalité, il ressortait des preuves que M^me^ Cole avait des difficultés à composer avec des déceptions relativement mineures, qu'elle souffrait d'un trouble dysthymique, et qu'elle avait une personnalité mal adaptée, ce qui la prédisposait à la dépression.

PROCEDURAL HISTORY

[18] By correspondence dated July 10, 2007, the DVA refused to grant Ms. Cole's application for a disability pension under paragraph 21(2)(*a*) of the *Pension Act*. In that correspondence, the DVA stated:

A review of your service medical records indicate that you were diagnosed and treated for Major Depression during your service period. However, there is a lack of documented and objective evidence to show that your military service duties or any other service factors caused or contributed to the development and/or aggravation (permanent worsening) of the claimed condition. [Emphasis added.]

[19] Dissatisfied with this decision, Ms. Cole asked for a review of it by an entitlement review panel, as permitted under the VRAB Act. In upholding the denial of her disability pension application, the entitlement review panel, on June 17, 2008, stated:

After having reviewed all of the evidence, the Board cannot conclude that service factors were the causative factors of the claimed condition and cannot see a permanent worsening from these factors. The Board cannot conclude that pension entitlement is indicated. [Emphasis added.]

[20] In July of 2012, Ms. Cole appealed the entitlement review panel's decision to the Board. In denying the appeal, the Board made the following findings:

The onus is on the Appellant to demonstrate to the Board that military factors caused and/or aggravated the claimed condition….

PROCÉDURES

[18] Par correspondance datée du 10 juillet 2007, le MAC a refusé la demande de pension d'invalidité que M^me^ Cole avait faite aux termes de l'alinéa 21(2)*a*) de la *Loi sur les pensions*. Dans cette correspondance, le MAC a affirmé :

[TRADUCTION] L'examen de vos dossiers médicaux relatifs au service indique qu'on vous a diagnostiqué une dépression majeure, pour laquelle vous avez été traitée, pendant votre période de service. Toutefois, il manque d'éléments de preuve documentés et objectifs démontrant que les fonctions afférentes à votre service militaire ou d'autres facteurs liés à votre service ont causé le développement de l'affection alléguée et/ou son aggravation (permanente) ou y ont contribué. [Non souligné dans l'original.]

[19] Insatisfaite de cette décision, M^me^ Cole en a demandé le réexamen par un comité de révision des décisions relatives à l'admissibilité, comme le permet la Loi sur le TACRA. Le comité de révision a confirmé le rejet de sa demande de pension d'invalidité le 17 juin 2008, en affirmant :

[TRADUCTION] Après avoir examiné tous les éléments de preuve, le Tribunal ne peut pas conclure que des facteurs liés au service ont causé l'affection alléguée et ne peut pas constater d'aggravation permanente causée par ces facteurs. Le Tribunal ne peut pas conclure qu'un droit à pension est indiqué. [Non souligné dans l'original.]

[20] En juillet 2012, M^me^ Cole a interjeté appel de la décision du comité de révision des décisions relatives à l'admissibilité auprès du Tribunal. Le Tribunal a rejeté l'appel, en tirant les conclusions suivantes :

[TRADUCTION] Le fardeau incombe à l'appelante de démontrer au Tribunal que des facteurs militaires ont causé et/ou aggravé l'affection alléguée […]

However, the Board was not convinced that these work issues were the source of her depression….

While work stressors are noted, they do not appear to take prevalence in the treatment sessions.…

However, without the evidence to establish that service factors caused or aggravated the claimed condition, the Board is regrettably unable to deliver a more favourable response at this time. [Emphasis added.]

[21] Ms. Cole applied to the Federal Court to review the Board's decision. The Federal Court Judge dismissed the application on the basis that the evidence before the Board was sufficient to support its conclusion that Ms. Cole's "medical condition was not caused by her military service" [at paragraph 50].

[22] In paragraph 25 of his reasons, the Federal Court Judge framed the issue before him as follows:

The sole issue before the Appeal Panel was whether the Applicant had established that her disability arose out of or was directly connected to her military service. This issue involves both the interpretation of the Appeal Panel's enabling statutes and the application of the law to the facts. This Court and the Federal Court of Appeal have confirmed on a number of occasions that the Appeal Board's weighing of the evidence and interpretation of its statutory scheme is reviewable on a standard of reasonableness.

[23] Although the Federal Court Judge acknowledged that the issue before him included the interpretation of the *Pension Act*, this excerpt from his reasons indicates that, in determining the standard of review, he characterized the question before him as one of mixed fact and law in respect of which there was no readily extricable legal issue of statutory interpretation.

[24] The Federal Court Judge addressed Ms. Cole's assertion that the Board erred by failing to explain its determination of the appropriate standard of causation mandated by the phrase "arose out of or was directly connected with" and how that standard applied to

Toutefois, le Tribunal n'a pas été convaincu que ces problèmes liés au travail avaient été la source de sa dépression […]

Bien que des facteurs de stress liés au travail soient notés, ils ne semblent pas jouer un rôle prépondérant lors des séances de traitement […]

Toutefois, sans la preuve permettant d'établir que des facteurs liés au service ont causé ou aggravé l'affection alléguée, le Tribunal ne peut malheureusement pas donner une réponse plus favorable à ce stade. [Non souligné dans l'original.]

[21] M[me] Cole a demandé à la Cour fédérale d'examiner la décision du Tribunal. Le juge de la Cour fédérale a rejeté la demande au motif que les éléments de preuve dont disposait le Tribunal allaient dans le sens de sa conclusion selon laquelle « l'affection médicale de [Mme Cole] ne découlait pas de son service militaire » [au paragraphe 50].

[22] Au paragraphe 25 de ses motifs, le juge de la Cour fédérale a formulé ainsi la question dont il était saisi :

La seule question que devait trancher le comité d'appel était de savoir si la demanderesse avait établi que son invalidité était consécutive à son service militaire ou y était rattachée directement. Pour trancher cette question, il faut interpréter la loi habilitante du comité d'appel et appliquer le droit aux faits. Notre Cour et la Cour d'appel fédérale ont confirmé à de nombreuses reprises que l'appréciation des éléments de preuve par le comité d'appel et l'interprétation qu'il fait de sa loi habilitante sont assujetties à la norme de la décision raisonnable.

[23] Bien que le juge de la Cour fédérale ait reconnu que la question dont il était saisi concernait notamment l'interprétation de la *Loi sur les pensions*, il ressort de l'extrait précité de ses motifs que, lorsqu'il a déterminé la norme de contrôle qu'il devait appliquer, il a qualifié la question dont il était saisi de question mélangée de fait et de droit qui ne soulevait aucune question d'interprétation des lois facilement isolable.

[24] Le juge de la Cour fédérale a discuté la thèse de M[me] Cole selon laquelle le Tribunal avait commis une erreur en omettant d'expliquer comment il avait conclu quelle norme de causalité correspondait à l'expression « consécutive ou rattachée directement [à] » et comment

Ms. Cole's circumstances. In doing so, he acknowledged that by virtue of section 2 of the *Pension Act* and section 3 of the VRAB Act (reproduced below), paragraph 21(2)(*a*) must be given a broad and generous interpretation.

[25] At paragraphs 34 to 36 of his reasons, the Federal Court Judge stated:

It is clear that the disease or injury (or the aggravation thereof) need not be directly connected to the military service, as the connecting word "or" is used in paragraph 21(2)(*a*) to link "directly connected" with "arose out of". At the same time, it would clearly not be sufficient for a claimant to solely show that he or she was serving in the armed forces at the time, as it would presumably be if the claim was made pursuant to paragraph 21(1)(*a*). This is precisely the conclusion reached by the Federal Court of Appeal in *Canada (Attorney General) v Frye*, 2005 FCA 264. In that case, the Court found that "… while it is not enough that the person was serving in the armed forces at the time, the causal nexus that a claimant must show between the death or injury and military service need be neither direct nor immediate" (at para 29). See also *Bradley v Canada (Attorney General)*, 2011 FC 309; *Hall v Canada (Attorney General)*, 2011 FC 1431.

In other words, I agree with the Applicant that paragraph 21(2)(*a*) does not require proof of a direct connection, but I disagree that some kind of causal connection would be sufficient or that military service was among the contributing causes of her disability [emphasis in original]. It seems to me that the words "arising out of" and the overall context of the statute call for something more than some nexus or causal connection, and require that the military service be the main and prevalent cause of the disease or injury, or at the very least a significant factor [emphasis added by Justice Ryer]. Another way of putting it might be to say that the injury or disease would not have occurred but for the military service. [Emphasis in original.]

This is precisely the standard that the Appeal Board applied in its decision. Even though the Appeal Board did not state explicitly the causation paradigm it was applying, it emerges from its analysis (and especially from the two quotes reproduced at paragraph 22 of these reasons) that it was not convinced the Applicant would not be suffering from major depression had it not been for the work stressors and the workplace difficulties she encountered through her military career. This interpretation of paragraph 21(2)(*a*) was clearly reasonable and consistent with the prevailing jurisprudence on this issue. The Appeal Board was not requiring the Applicant

cette norme s'appliquait à la situation de M^me^ Cole. Le juge de la Cour fédérale a ainsi reconnu que l'article 2 de la *Loi sur les pensions* et l'article 3 de la Loi sur le TACRA (reproduits ci-dessous) appelaient une interprétation libérale et générale de l'alinéa 21(2)*a*).

[25] Aux paragraphes 34 à 36 de ses motifs, le juge de la Cour fédérale a observé :

Il est clair que la maladie ou la blessure (ou leur aggravation) doit être directement liée au service militaire, comme en témoigne la conjonction « ou » à l'alinéa 21(2)*a*) qui vient lier l'expression « rattachée directement » à « consécutive ». En même temps, il va de soi qu'un demandeur ne pourrait se contenter de démontrer qu'il servait dans les Forces armées durant la période pertinente, ce qui est implicite si la demande est présentée au titre de l'alinéa 21(1)*a*). C'est précisément la conclusion à laquelle la Cour d'appel fédérale est parvenue dans l'arrêt *Canada (Procureur général) c Frye*, 2005 CAF 264. Dans cette affaire, la Cour a estimé que « […] même s'il ne suffit pas de prouver que la personne servait dans les Forces armées à l'époque, il n'est pas nécessaire que le demandeur établisse un lien de causalité direct ou immédiat entre le décès ou la blessure et le service militaire » (au paragraphe 29). Voir également *Bradley c Canada (Procureur général)*, 2011 CF 309; *Hall c Canada (Procureur général)*, 2011 CF 1431.

En d'autres termes, je conviens avec la demanderesse que l'alinéa 21(2)*a*) n'exige pas de prouver un lien direct, mais je ne pense pas qu'il suffise d'établir une certaine forme de lien de causalité ou que le service militaire ait été l'une des causes qui ont contribué à son invalidité [souligné dans l'original]. Il me semble, que le terme « consécutive » et le contexte général de la loi exigent qu'il soit démontré davantage qu'un certain lien ou rapport causal, et que le service militaire doit être la cause principale ou prédominante de la maladie ou de la blessure, ou à tout le moins avoir joué un rôle significatif [soulignement ajouté par le juge Ryer]. On pourrait sans doute tout aussi bien dire qu'il doit être établi que la blessure ou la maladie ne serait pas survenue n'eût été le service militaire. [Souligné dans l'original.]

C'est exactement la norme que le comité d'appel a appliquée dans sa décision. Bien qu'il n'ait pas explicitement énoncé le concept de causalité qu'il a retenu, il ressort de son analyse (et notamment des deux extraits reproduits au paragraphe 22 des présents motifs) qu'il n'était pas convaincu que la demanderesse ne souffrirait pas de toute façon de dépression majeure si elle n'avait pas été exposée aux facteurs de stress liés à son travail et les difficultés professionnelles rencontrées tout au long de sa carrière militaire. L'interprétation de l'alinéa 21(2)*a*) était manifestement raisonnable et conforme à la jurisprudence applicable en cette matière. Contrairement à

to prove sole or direct causation, as alleged by the Applicant, but was looking for evidence that the military factors played a primary or major role in the aggravation or onset of her claimed condition. In doing so, the Appeal Board made no reviewable error. [Emphasis added.]

[26] These paragraphs make it clear that the Federal Court Judge was considering the causative requirements of only the words "arose out of" and not the words "directly connected with" in paragraph 21(2)(*a*) of the *Pension Act*. In paragraph 35 of his reasons, he appears to conclude that "arose out of" required military service to be "the main or prevalent cause" or "at the very least a significant factor." However, in paragraph 36 he concludes that the Board interpreted "arose out of" as requiring Ms. Cole's military service to be the "primary or major cause" of her depression, and then found that in using that interpretation, the Board made no reviewable error.

[27] In dismissing Ms. Cole's application on the basis that the Board had sufficient evidence before it that Ms. Cole's claimed condition—her depression—was not caused by her military service, the Federal Court Judge reiterated his conclusion that the phrase "arose out of or was directly connected with" requires a "primary cause" degree or level of causation.

ISSUES

[28] In reviewing a decision of the Federal Court in an application for judicial review of the decision of an administrative tribunal, this Court must determine whether the reviewing court correctly determined the standard of review by which it reviewed the decision of the tribunal. (See *Agraira v. Canada (Public Safety and Emergency Preparedness)*, 2013 SCC 36, [2013] 2 S.C.R. 559, at paragraphs 45 to 47.) If so, then this Court must determine whether the reviewing court correctly applied the appropriate standard. In this regard, the

ce qu'elle affirme, le comité d'appel n'attendait pas d'elle qu'elle établisse un lien causal unique ou direct, mais qu'elle prouve que les facteurs militaires avaient joué un rôle principal ou majeur dans l'aggravation ou l'apparition de l'affection alléguée. Ce faisant, le comité d'appel n'a commis aucune erreur susceptible de contrôle. [Soulignement ajouté.]

[26] Il ressort clairement de ces passages que le juge de la Cour fédérale examinait seulement les exigences relatives au lien de causalité au regard des mots « consécutive [à] », et non celles au regard des mots « rattachée directement [à] », toutes deux employées à l'alinéa 21(2)*a*) de la *Loi sur les pensions*. Au paragraphe 35 de ses motifs, il semble conclure que « consécutive [à] » exigeait que le service militaire soit « la cause principale ou prédominante » ou « à tout le moins [qu'il ait] joué un rôle significatif ». Toutefois, au paragraphe 36, il conclut que le Tribunal a interprété « consécutive à » comme exigeant que le service militaire de M^me^ Cole soit la « cause principale ou majeure » de sa dépression, puis il conclut qu'en retenant cette interprétation, le Tribunal n'a commis aucune erreur susceptible de contrôle.

[27] Lorsqu'il a rejeté la demande de M^me^ Cole au motif que le Tribunal disposait de suffisamment d'éléments de preuve pour pouvoir conclure que l'affection alléguée de M^me^ Cole — sa dépression — n'avait pas été causée par son service militaire, le juge de la Cour fédérale a réitéré sa conclusion selon laquelle l'expression « consécutive ou rattachée directement [à] » exige un degré ou niveau de causalité correspondant à une « cause principale ».

QUESTIONS EN LITIGE

[28] La Cour, lorsqu'elle examine une décision de la Cour fédérale par laquelle cette dernière statue sur une décision d'un tribunal administratif, doit rechercher si la cour réformatrice a retenu la norme de contrôle appropriée à l'égard de la décision du tribunal administratif (voir *Agraira c. Canada (Sécurité publique et Protection civile)*, 2013 CSC 36, [2013] 2 R.C.S. 559, aux paragraphes 45 à 47). Dans l'affirmative, la Cour doit alors rechercher si la cour réformatrice a appliqué correctement la norme appropriée. À cet égard, on dit souvent

appellate court is often described as "step[ping] into the shoes" of the reviewing court (see *Attaran v. Canada (Attorney General)*, 2015 FCA 37, 380 D.L.R. (4th) 737, at paragraph 9).

[29] If this Court determines that the Federal Court Judge has incorrectly determined or applied the applicable standard, then we must intervene and conduct the necessary review.

[30] In conducting his review, the Federal Court Judge determined that there were two issues before the Board which, in my view, may be summarized as follows:

(a) whether the Board erred in interpreting the phrase "arose out of or was directly connected with", in paragraph 21(2)(*a*) of the *Pension Act*, as requiring an applicant for a disability pension to establish that his or her military service was the primary cause of the claimed condition (the interpretative issue); and

(b) whether the Board erred in assessing the evidence and in finding that Ms. Cole is not entitled to a pension under paragraph 21(2)(*a*) of the *Pension Act* (the application of evidence issue).

[31] Thus, the issues in this appeal are:

(a) Did the Federal Court Judge err in selecting reasonableness as the standard of review with respect to the interpretative issue?

(b) If correctness is the required standard of review with respect to the interpretative issue, what is the correct interpretation of the causal connection requirement of the phrase "directly connected with" in paragraph 21(2)(*a*) of the *Pension Act*?

que la Cour d'appel [fédérale] « se [met] à la place » de la cour réformatrice (voir *Attaran c. Canada (Procureur général)*, 2015 CAF 37, au paragraphe 9).

[29] Si notre Cour conclut que le juge de la Cour fédérale a commis une erreur dans le choix de la norme de contrôle ou dans son application, elle doit intervenir et procéder au contrôle nécessaire.

[30] Lorsqu'il a effectué son contrôle, le juge de la Cour fédérale a conclu que le Tribunal avait été saisi de deux questions, que l'on peut résumer ainsi :

a) le Tribunal a-t-il commis une erreur lorsqu'il a interprété les mots « consécutive ou rattachée directement [à] », à l'alinéa 21(2)*a*) de la *Loi sur les pensions*, comme exigeant que le demandeur d'une pension d'invalidité établisse que son service militaire a été la cause principale de l'affection alléguée (la question d'interprétation)?

b) le Tribunal a-t-il commis une erreur lorsqu'il a apprécié les éléments de preuve et a conclu que M^me^ Cole n'avait pas droit à une pension sous le régime de l'alinéa 21(2)*a*) de la *Loi sur les pensions* (la question relative à l'application de la loi aux éléments de preuve)?

[31] En conséquence, les questions à trancher dans le présent appel sont les suivantes :

a) Le juge de la Cour fédérale a-t-il commis une erreur lorsqu'il a conclu que la norme de contrôle applicable à la question d'interprétation était la norme de la décision raisonnable?

b) Si la norme de contrôle applicable à la question d'interprétation est la norme de la décision correcte, quelle est l'interprétation correcte de l'exigence de causalité correspondant aux mots « rattachée directement [à] » à l'alinéa 21(2)*a*) de la *Loi sur les pensions*?

(c) If reasonableness is the required standard of review with respect to the interpretative issue, was the primary cause interpretation of the causal connection requirement of the phrase "directly connected with", in paragraph 21(2)(*a*) of the *Pension Act*, reasonable?

(d) Did the Board err in its determination of the application of evidence issue?

ANALYSIS

A. Did the Federal Court Judge select the correct standard of review with respect to the interpretative issue?

Statutory context

[32] Subsections 21(1) and (2) of the *Pension Act* permit awards of pensions in respect of military service. The relevant portions of those provisions read as follows:

Service during war, or special duty service

21. (1) In respect of service rendered during World War I, service rendered during World War II other than in the non-permanent active militia or the reserve army, service in the Korean War, service as a member of the special force, and special duty service,

(*a*) where a member of the forces suffers disability resulting from an injury or disease or an aggravation thereof that was attributable to or was incurred during such military service, a pension shall, on application, be awarded to or in respect of the member in accordance with the rates for basic and additional pension set out in Schedule I;

(*b*) where a member of the forces dies as a result of an injury or disease or an aggravation thereof that was attributable to or was incurred during such military service, a pension shall be awarded in respect of the member in accordance with the rates set out in Schedule II;

…

c) Si la norme de contrôle applicable à la question d'interprétation est la norme de la décision raisonnable, l'interprétation des mots « rattachée directement [à] » à l'alinéa 21(2)*a*) de la *Loi sur les pensions* comme exigeant une causalité correspondant au critère de la cause principale était-elle raisonnable?

d) Le Tribunal a-t-il commis une erreur dans son application de la loi aux éléments de preuve?

ANALYSE

A. Le juge de la Cour fédérale a-t-il retenu la norme de contrôle correcte relativement à la question d'interprétation?

Les textes législatifs pertinents

[32] Les paragraphes 21(1) et (2) de la *Loi sur les pensions* permettent d'accorder des pensions pour le service militaire. Les parties pertinentes de ces dispositions disposent :

Service pendant la guerre ou en service spécial

21. (1) Pour le service accompli pendant la Première Guerre mondiale ou la Seconde Guerre mondiale, sauf dans la milice active non permanente ou dans l'armée de réserve, le service accompli pendant la guerre de Corée, le service accompli à titre de membre du contingent spécial et le service spécial :

a) des pensions sont, sur demande, accordées aux membres des forces ou à leur égard, conformément aux taux prévus à l'annexe I pour les pensions de base ou supplémentaires, en cas d'invalidité causée par une blessure ou maladie — ou son aggravation — survenue au cours du service militaire ou attribuable à celui-ci;

b) des pensions sont accordées à l'égard des membres des forces, conformément aux taux prévus à l'annexe II, en cas de décès causé par une blessure ou maladie — ou son aggravation — survenue au cours du service militaire ou attribuable à celui-ci;

[…]

Service in militia or reserve army and in peace time

(2) In respect of military service rendered in the non-permanent active militia or in the reserve army during World War II and in respect of military service in peace time,

(*a*) where a member of the forces suffers disability resulting from an injury or disease or an aggravation thereof that arose out of or was directly connected with such military service, a pension shall, on application, be awarded to or in respect of the member in accordance with the rates for basic and additional pension set out in Schedule I;

(*b*) where a member of the forces dies as a result of an injury or disease or an aggravation thereof that arose out of or was directly connected with such military service, a pension shall be awarded in respect of the member in accordance with the rates set out in Schedule II;

Milice active non permanente ou armée de réserve en temps de paix

(2) En ce qui concerne le service militaire accompli dans la milice active non permanente ou dans l'armée de réserve pendant la Seconde Guerre mondiale ou le service militaire en temps de paix :

a) des pensions sont, sur demande, accordées aux membres des forces ou à leur égard, conformément aux taux prévus à l'annexe I pour les pensions de base ou supplémentaires, en cas d'invalidité causée par une blessure ou maladie — ou son aggravation — consécutive ou rattachée directement au service militaire;

b) des pensions sont accordées à l'égard des membres des forces, conformément aux taux prévus à l'annexe II, en cas de décès causé par une blessure ou maladie — ou son aggravation — consécutive ou rattachée directement au service militaire;

[33] In interpreting these and any other provisions of the *Pension Act*, it is important to consider and apply the interpretative mandate contained in section 2 of the *Pension Act*, which reads as follows:

[33] Lorsque l'on interprète ces dispositions et toutes les autres dispositions de la *Loi sur les pensions*, il importe de prendre en compte et d'appliquer la directive d'interprétation énoncée à l'article 2 de la *Loi sur les pensions*, qui est ainsi rédigé :

Construction

2. The provisions of this Act shall be liberally construed and interpreted to the end that the recognized obligation of the people and Government of Canada to provide compensation to those members of the forces who have been disabled or have died as a result of military service, and to their dependants, may be fulfilled.

Règle d'interprétation

2. Les dispositions de la présente loi s'interprètent d'une façon libérale afin de donner effet à l'obligation reconnue du peuple canadien et du gouvernement du Canada d'indemniser les membres des forces qui sont devenus invalides ou sont décédés par suite de leur service militaire, ainsi que les personnes à leur charge.

[34] A similar interpretative mandate is contained in section 3 of the VRAB Act, which reads as follows:

[34] Une directive d'interprétation similaire est énoncée à l'article 3 de la Loi sur le TACRA, qui dispose :

Construction

3. The provisions of this Act and of any other Act of Parliament or of any regulations made under this or any other Act of Parliament conferring or imposing jurisdiction, powers, duties or functions on the Board shall be liberally construed and interpreted to the end that the recognized obligation of the people and Government of Canada to those who have served their country so well and to their dependants may be fulfilled.

Principe général

3. Les dispositions de la présente loi et de toute autre loi fédérale, ainsi que de leurs règlements, qui établissent la compétence du Tribunal ou lui confèrent des pouvoirs et fonctions doivent s'interpréter de façon large, compte tenu des obligations que le peuple et le gouvernement du Canada reconnaissent avoir à l'égard de ceux qui ont si bien servi leur pays et des personnes à leur charge.

[35] Subsection 21(1) of the *Pension Act* applies in respect of services rendered during war or special duty

[35] Le paragraphe 21(1) de la *Loi sur les pensions* vise le service accompli durant la guerre et au service

service. The language in subsection 21(1) of the *Pension Act* requires that the injury, disease or death of a serviceman or woman and his or her wartime or special duty military service must be "attributable to" or "incurred during" such military service. This level of connectivity has been referred to as the "insurance principle", reflecting a desire on the part of Parliament to provide "full coverage" pension protection to men and women exposed to risks when serving their country during wartime or special duty service (see May 27, 1941, Hansard [*House of Commons Debates*, 19th Parl., 2nd Sess., Vol. III], at page 3167). Thus, the phrase "attributable to" contemplates a degree of causal connection between the death, injury or disease and the wartime or special duty service, while the phrase "was incurred during" contemplates only a temporal connection.

[36] Subsection 21(2) of the *Pension Act* applies in respect of service in the militia or reserve army in peace time. The connectivity language in subsection 21(2) of the *Pension Act* with respect to injury, disease or death of a serviceman or woman and his or her peace time military service is "arose out of or was directly connected with" such military service. This language was introduced in 1941, reflecting Parliament's intention to provide less than "full coverage" pension protection in respect of risks to which men and women may be exposed when serving their country in peace time. Thus, it appears that the phrase "arose out of or was directly connected with" requires a higher degree of causal connection between the death, injury or disease and the peace time military service than is required by the phrase "attributable to or incurred during" in subsection 21(1) of the *Pension Act.*

The paragraph 21(2)(a) requirements

[37] Establishing entitlement to a disability pension under paragraph 21(2)(*a*) of the *Pension Act* is a four-step process:

spécial. Les dispositions du paragraphe 21(1) de la *Loi sur les pensions* exigent que la blessure, la maladie ou le décès d'un militaire et son service militaire accompli durant la guerre ou en service spécial soient « survenu[s] au cours » de ce service militaire ou soient « attribuable[s] à celui-ci ». Ce degré de causalité a été désigné comme le [TRADUCTION] « principe de l'assurance », traduisant le désir du législateur d'assurer, en fait de protection par voie de prestations, une [TRADUCTION] « couverture complète » aux hommes et aux femmes qui ont été exposés à des risques alors qu'ils servaient leur pays pendant la guerre ou en service spécial (voir le Hansard [*Débats de la Chambre des communes*, 19e lég., 2e sess., vol. III], à la page 3237, 27 mai 1941). Ainsi, les mots « attribuable à » évoquent un degré de causalité entre, d'une part, le décès, la blessure ou la maladie, et d'autre part, le service pendant la guerre ou le service spécial, tandis que les mots « survenue au cours » évoquent seulement un lien temporel.

[36] Le paragraphe 21(2) de la *Loi sur les pensions* s'applique relativement au service dans la milice ou dans l'armée de réserve en temps de paix. Au paragraphe 21(2) de la *Loi sur les pensions*, le lien entre la blessure, la maladie ou le décès d'un militaire et son service militaire en temps de paix est évoqué par l'expression « consécutive ou rattachée directement [à] » ce service militaire. La disposition comportant cette expression a été promulguée en 1941, et elle traduit l'intention du législateur d'assurer, en fait de protection au moyen de prestations, moins qu'une [TRADUCTION] « couverture complète » relativement aux risques auxquels des hommes et des femmes peuvent être exposés alors qu'ils servent leur pays en temps de paix. Ainsi, il appert que les mots « consécutive ou rattachée directement [à] » exigent un degré plus élevé de causalité entre, d'une part, le décès, la blessure ou la maladie, et d'autre part, le service militaire en temps de paix, que ce qu'exigent les mots « survenue au cours […] ou attribuable à » au paragraphe 21(1) de la *Loi sur les pensions*.

Les exigences de l'alinéa 21(1)a)

[37] L'établissement du droit à une pension d'invalidité en vertu de l'alinéa 21(2)*a*) de la *Loi sur les pensions* est un processus comportant quatre étapes :

(a) Step one requires the applicant to demonstrate that he or she has a claimed condition—an injury or disease, or an aggravation thereof.

(b) Step two requires the applicant to demonstrate that the claimed condition "arose out of or was directly connected with" his or her service as a member of the forces.

(c) Step three requires the applicant to establish that he or she suffers from a disability.

(d) Step four requires the applicant to establish that his or her disability resulted from a military service-related claimed condition.

[38] While there is no statutory mandate to conduct the inquiry in this sequence, it seems logical to me, in the particular circumstances of this case, that the establishment of the existence of the claimed condition would precede the establishment of the existence of the disability. Indeed, this approach appears to have been followed by the Board in the instant circumstances.

[39] Disability is defined in subsection 3(1) of the *Pension Act* as follows:

Definitions **3.** …

"disability" « *invalidité* » "disability" means the loss or lessening of the power to will and to do any normal mental or physical act;

This definition of disability is important as it is a distinct element that must be established in step three and must not be conflated with the claimed condition that the applicant must establish in step one.

[40] Steps one and three require factual determinations as to the existence of the claimed condition and the disability. In the circumstances under consideration, there is no issue as to whether Ms. Cole suffers from major depression—the claimed condition—as it was one of the reasons for her discharge from the forces. However, there was no finding with respect to step three

a) La première étape exige que le demandeur démontre qu'il a une affection alléguée — une blessure ou une maladie ou une aggravation de celle-ci.

b) La deuxième étape exige que le demandeur démontre que l'affection alléguée est « consécutive ou rattachée directement [à] » son service en tant que membre des forces.

c) La troisième étape exige que le demandeur établisse qu'il souffre d'une invalidité.

d) La quatrième étape exige que le demandeur établisse que son invalidité découle d'une affection alléguée reliée au service militaire.

[38] La loi n'exige pas que la recherche soit menée selon cette séquence, mais il me paraît logique, dans les circonstances particulières de l'espèce, que l'établissement de l'existence de l'affection alléguée précède l'établissement de l'existence de l'invalidité. D'ailleurs, le Tribunal semble avoir adopté cette démarche en l'espèce.

[39] Le paragraphe 3(1) de la *Loi sur les pensions* définit ainsi le mot « invalidité » :

3. […] Définitions

« invalidité » La perte ou l'amoindrissement de la faculté de vouloir et de faire normalement des actes d'ordre physique ou mental. « invalidité » "*disability*"

Cette définition de l'invalidité est importante, car il s'agit d'un élément distinct qui doit être établi à la troisième étape et qui ne doit pas être confondu avec l'affection alléguée que le demandeur doit établir à la première étape.

[40] Les première et troisième étapes exigent des déterminations de faits quant à l'existence de l'affection alléguée et de l'invalidité. En l'espèce, il est constant que M^me^ Cole souffre d'une dépression majeure — l'affection alléguée — puisqu'il s'agissait de l'une des raisons pour lesquelles elle avait été libérée des forces. Toutefois, il n'y a eu aucune conclusion relativement

because the Board found that the requirements of step two had not been fulfilled.

[41] Both of steps two and four contain causal connection requirements. In step four, the applicant must show a causal connection between the military service-related claimed condition, established in steps one and two, and the applicant's disability that is established in step three. The nature and extent of this causal connection requirement are not in issue in this appeal. The Board never got to step three because it determined that Ms. Cole had not established the causal connection required by step two.

What standard of review did the Federal Court Judge select: correctness or reasonableness?

[42] In paragraph 25 of his reasons, the Federal Court Judge determined that the issue before the Board "was whether the Applicant had established that her disability arose out of or was directly connected to her military service" (my emphasis). With respect, this formulation of the issue conflated the "injury or disease", the claimed condition that is required to be established in step one of the disability pension entitlement process, with the "disability" that must be established in step three of that process.

[43] The Federal Court Judge went on to state that the resolution of the issue that he formulated involves both an interpretation of the *Pension Act* and the application of that interpretation to the facts. In referring to both the interpretation and application of the legal standard as part of a single issue, it appears to me that the Federal Court Judge concluded that the issue before the Board was one of mixed fact and law, which typically attracts review on the standard of reasonableness.

[44] Applying the reasonableness standard to questions of mixed fact and law is usually appropriate, but may not be if the interpretation of the applicable legal

à la troisième étape, parce que le Tribunal a conclu qu'il n'avait pas été satisfait aux exigences de la deuxième étape.

[41] Les deuxième et quatrième étapes exigent toutes deux un lien de causalité. À la quatrième étape, le demandeur doit démontrer un lien de causalité entre l'affection alléguée reliée au service militaire, établie aux première et deuxième étapes, et l'invalidité du demandeur qui est établie à la troisième étape. La nature et la portée de cette exigence de causalité ne sont pas en cause dans le présent appel. Le Tribunal n'est pas parvenu à la troisième étape parce qu'il a conclu que M^me^ Cole n'avait pas établi le lien de causalité exigé à la deuxième étape.

Quelle norme de contrôle le juge de la Cour fédérale a-t-il retenue : la norme de la décision correcte ou celle de la décision raisonnable?

[42] Au paragraphe 25 de ses motifs, le juge de la Cour fédérale a conclu que la question dont le Tribunal avait été saisi « était de savoir si la demanderesse avait établi que son invalidité était consécutive à son service militaire ou y était rattachée directement » (non souligné dans l'original). Avec égards, cette formulation de la question confondait la « blessure ou maladie » — l'affection alléguée qui doit être établie à la première étape du processus d'établissement du droit à une pension d'invalidité — avec l'« invalidité », laquelle doit être établie à la troisième étape de ce processus.

[43] Le juge de la Cour fédérale a ensuite observé que, pour résoudre la question qu'il avait formulée, il fallait interpréter la *Loi sur les pensions* et appliquer cette interprétation aux faits. En évoquant l'interprétation et l'application du critère légal comme faisant partie d'une seule et même question, je crois que le juge de la Cour fédérale a conclu que la question dont le Tribunal avait été saisi était une question mélangée de fait et de droit, qui commande généralement un examen selon la norme de la raisonnabilité.

[44] Il est habituellement approprié d'appliquer la norme de la décision raisonnable aux questions mélangées de fait et de droit, mais il peut en aller autrement

provision is in dispute and is discrete enough to be analysed separately.

[45] The interpretation of the phrase "arose out of or was directly connected with" in paragraph 21(2)(*a*) of the *Pension Act* is a question of law that was in dispute before the Board. In my view, that question was a discrete question of law capable of being considered separately. Indeed, the Federal Court Judge did deal with the interpretation of this phrase in paragraphs 28 to 36 of his reasons when he considered the appropriate level of causal connection that was required under paragraph 21(2)(*a*) of the *Pension Act*. However, in doing so, the Federal Court Judge applied the reasonableness standard, not the correctness standard, in his review of the Board's interpretation of this phrase.

The correct standard of review: correctness or reasonableness?

[46] Before this Court, the appellant argued that this interpretative question should be reviewed on the standard of correctness. The respondent agreed that with respect to pure questions of law, including those readily extricable from questions of mixed fact and law, correctness should be the standard.

[47] While recent jurisprudence tends to provide deference to experienced tribunals when they interpret their "home statute", this is not a rule of universal application. In *Dunsmuir v. New Brunswick*, 2008 SCC 9, [2008] 1 S.C.R. 190, the Supreme Court of Canada held that if prior jurisprudence has satisfactorily determined the applicable standard of review, with respect to a particular category of question, it is unnecessary to engage in any further standard of review analysis.

[48] In particular, in paragraph 62 of *Dunsmuir*, Justices Bastarache and LeBel, speaking for the majority, stated:

lorsque l'interprétation de la disposition législative applicable est controversée et que cette interprétation constitue une question assez distincte pour pouvoir être analysée séparément.

[45] L'interprétation des mots « consécutive ou rattachée directement [à] » à l'alinéa 21(2)*a*) de la *Loi sur les pensions* est une question de droit qui était controversée devant le Tribunal. À mon avis, il s'agissait d'une question de droit distincte susceptible d'être examinée séparément. De fait, le juge de la Cour fédérale a discuté de l'interprétation de cette expression aux paragraphes 28 à 36 de ses motifs lorsqu'il a examiné la question du degré de causalité qui était exigé aux termes de l'alinéa 21(2)*a*) de la *Loi sur les pensions*. Toutefois, ce faisant, le juge de la Cour fédérale a appliqué la norme de la décision raisonnable, et non celle de la décision correcte, dans le cadre de son examen de l'interprétation que le Tribunal avait faite de ce membre de phrase.

La norme de contrôle applicable : la norme de la décision correcte ou celle de la décision raisonnable?

[46] Devant la Cour, l'appelante a soutenu que cette question d'interprétation devait être examinée selon la norme de la décision correcte. L'intimé a convenu qu'à l'égard des pures questions de droit, y compris celles qui peuvent être facilement isolées des questions mélangées de fait et de droit, c'est généralement la norme de la décision correcte qui s'applique.

[47] Bien que la jurisprudence récente tende à préconiser la retenue à l'égard des tribunaux expérimentés lorsqu'ils interprètent leur « loi constitutive », il ne s'agit pas d'une règle d'application universelle. L'arrêt *Dunsmuir c. Nouveau-Brunswick*, 2008 CSC 9, [2008] 1 R.C.S. 190, rendu par la Cour suprême du Canada, enseigne que, si la jurisprudence détermine déjà de manière satisfaisante quelle est la norme de contrôle applicable relativement à une catégorie de questions en particulier, il n'est pas nécessaire de pousser plus loin l'analyse de la norme de contrôle.

[48] En particulier, au paragraphe 62 de l'arrêt *Dunsmuir*, les juges Bastarache et LeBel, s'exprimant au nom de la majorité, ont observé :

In summary, the process of judicial review involves two steps. First, courts ascertain whether the jurisprudence has already determined in a satisfactory manner the degree of deference to be accorded with regard to a particular category of question. Second, where the first inquiry proves unfruitful, courts must proceed to an analysis of the factors making it possible to identify the proper standard of review. [Emphasis added.]

[49] The continuing application of this approach has been reconfirmed by the Supreme Court of Canada in *Agraira v. Canada (Public Safety and Emergency Preparedness)*, 2013 SCC 36, [2013] 2 S.C.R. 559 [cited above], at paragraph 49.

[50] In *Frye v. Canada (Attorney General)*, 2005 FCA 264, 338 N.R. 382, this Court considered the question of the standard of causation that is required by the phrase "arose out of or was directly connected with" in paragraph 21(2)(*b*) of the *Pension Act*. The Court determined that the interpretation of this phrase was a question of law that was to be reviewed on the standard of correctness.

[51] In my view, the determination by this Court in *Frye* that the correctness standard must be used in considering the interpretation of the phrase "arose out of or was directly connected with" in paragraph 21(2)(*b*) of the *Pension Act* can be regarded as a satisfactory determination of the applicability of the correctness standard to the interpretation of those exact words in paragraph 21(2)(*a*), as required in this appeal.

[52] Moreover, I am of the view that the discernment of the standard of causation that was intended by Parliament when it enacted the phrase "arose out of or was directly connected with" in paragraph 21(2)(*a*) of the *Pension Act*, is a question of importance that extends beyond the ambit of the *Pension Act*. Questions of causation often arise in many other areas of law, including insurance, torts and workers' compensation. Additionally, it is my view that discerning degrees of causal connection—in marked contrast to applying such levels of causal connection, once discerned—is not a matter with

Bref, le processus de contrôle judiciaire se déroule en deux étapes. Premièrement, la cour de révision vérifie si la jurisprudence établit déjà de manière satisfaisante le degré de déférence correspondant à une catégorie de questions en particulier. En second lieu, lorsque cette démarche se révèle infructueuse, elle entreprend l'analyse des éléments qui permettent d'arrêter la bonne norme de contrôle. [Non souligné dans l'original.]

[49] La Cour suprême a reconfirmé que cette démarche était encore d'actualité à l'occasion de l'affaire *Agraira c. Canada (Sécurité publique et Protection civile)*, 2013 CSC 36, [2013] 2 R.C.S. 559 [précité], au paragraphe 49.

[50] À l'occasion de l'affaire *Frye c. Canada (Procureur général)*, 2005 CAF 264, notre Cour a examiné la question de la norme de causalité exigée par les mots « consécutive ou rattachée directement [à] » à l'alinéa 21(2)*b*) de la *Loi sur les pensions*. La Cour a conclu que l'interprétation de ces mots était une question de droit qui devait être examinée selon la norme de la décision correcte.

[51] À mon avis, l'enseignement de notre Cour par la jurisprudence *Frye* selon lequel il faut appliquer la norme de la décision correcte lors de l'examen de l'interprétation des mots « consécutive ou rattachée directement [à] » à l'alinéa 21(2)*b*) de la *Loi sur les pensions* peut être considéré comme une conclusion saine quant à l'applicabilité de la norme de la décision correcte à l'interprétation de ces mêmes mots à l'alinéa 21(2)*a*), soit la mission qui incombe à la Cour dans le présent appel.

[52] En outre, je suis d'avis que la détermination de la norme de causalité que le législateur a voulu établir en promulguant les mots « consécutive ou rattachée directement [à] » à l'alinéa 21(2)*a*) de la *Loi sur les pensions* est une question d'importance qui déborde le cadre de la *Loi sur les pensions*. Les questions de causalité se posent souvent dans de nombreux domaines du droit, notamment en matière d'assurance, de responsabilité civile délictuelle et d'indemnisation des accidentés du travail. De plus, je suis d'avis que le Tribunal n'est pas régulièrement appelé à discerner des degrés de causalité

which the Board would regularly grapple. That task, in my view, is one that courts are better suited to perform.

[53] The expertise of the Board with respect to this type of interpretative question stands in marked contrast to the expertise that many tribunals develop with respect to the interpretation of technical provisions of their home statute. For example, when setting freight rates with respect to the shipment of western grain, the Canadian Transportation Agency has to interpret such esoteric terms as the "volume-related composite price index". Clearly, much deference is owed to that Agency in the interpretation of that provision of its home statute.

[54] Similarly, Part V [sections 74 to 78] of the *Pension Act* provides for annual adjustments of pensions and allowances on the basis of a number of factors stipulated in that Part. In such circumstances, significant deference should be accorded to the Board in relation to its interpretation and application of the factors upon which such annual adjustments are based.

[55] In addition, in the recent decision of this Court in *Wilson v. Atomic Energy of Canada Limited*, 2015 FCA 17, [2015] 4 F.C.R. 468, Justice Stratas concluded that the standard of correctness was properly applicable in reviewing the decision of a labour arbitrator in relation to an interpretation of certain provisions of the *Canada Labour Code*, R.S.C., 1985, c. L-2.

[56] In that case, the Court concluded [at paragraph 52] that a "persistent discord" amongst labour arbitrators in respect of the interpretation of a particular provision of that legislation required the Court to review and resolve the interpretative issue by reference to the standard of correctness.

[57] As more fully addressed later in these reasons, there is disagreement, particularly at the Federal Court level, as to the causal connection requirements of the phrase "arose out of or was directly connected with" in paragraph 21(2)(*a*) of the *Pension Act*. Thus, I conclude that the logic applied by this Court in *Atomic Energy of*

— par contraste marqué avec l'application de ces degrés de causalité, une fois discernés. Je suis d'avis que le juge judiciaire est mieux à même de remplir cette mission.

[53] La compétence spécialisée du Tribunal à l'égard de ce type de question d'interprétation se démarque nettement de la compétence spécialisée que bon nombre de tribunaux acquièrent relativement à l'interprétation de dispositions techniques de leur loi constitutive. Par exemple, lorsqu'il fixe les tarifs de fret relativement au grain de l'Ouest, l'Office des transports du Canada doit interpréter des mots ésotériques comme « indice des prix composite afférent au volume ». Il y a évidemment lieu de faire preuve d'une grande retenue à l'égard de cet office lorsqu'il interprète cette disposition de sa loi constitutive.

[54] Dans le même ordre d'idées, la partie V [articles 74 à 78] de la *Loi sur les pensions* prévoit des ajustements annuels des pensions et des allocations en fonction de différents facteurs prévus dans cette partie de la Loi. Lorsque le Tribunal interprète et applique les facteurs sur lesquels se fondent ces ajustements annuels, il y a lieu de faire preuve d'une grande retenue.

[55] De plus, par l'arrêt récent *Wilson c. Énergie atomique du Canada limitée*, 2015 CAF 17, [2015] 4 R.C.F. 468, le juge Stratas a conclu que la norme de la décision correcte avait été appliquée à juste titre lors de l'examen de la décision d'un arbitre du travail concernant une interprétation de certaines dispositions du *Code canadien du travail*, L.R.C. (1985), ch. L-2.

[56] À l'occasion de cette affaire, la Cour a conclu [au paragraphe 52] qu'un « désaccord persistant » entre arbitres du travail concernant l'interprétation d'une certaine disposition de cette loi exigeait que la Cour examine et réponde à la question d'interprétation en fonction de la norme de la décision correcte.

[57] Comme je le discuterai plus en détail ultérieurement dans les présents motifs, il y a une controverse, en particulier au sein de la Cour fédérale, quant à savoir quelles exigences de causalité précises correspondent aux mots « consécutive ou rattachée directement [à] » à l'alinéa 21(2)*a*) de la *Loi sur les pensions*. J'en conclus

Canada Limited provides further support for my selection of the correctness standard of review with respect to the interpretative issue.

[58] In *McLean v. British Columbia (Securities Commission)*, 2013 SCC 67, [2013] 3 S.C.R. 895, Moldaver J. states, at paragraph 33:

> The answer, as this Court has repeatedly indicated since *Dunsmuir*, is that the resolution of unclear language in an administrative decision maker's home statute is usually best left to the decision maker. That is so because the choice between multiple reasonable interpretations will often involve policy considerations that we presume the legislature desired *the administrative decision maker* — not the courts — to make. Indeed, the exercise of that interpretative discretion is part of an administrative decision maker's "expertise". [Emphasis added; italics in original.]

[59] This passage indicates that there can be cases in which the standard of correctness is properly applicable with respect to the interpretation of the "home statute" of a tribunal. And, for the reasons that I have given, I conclude that this is one of those cases. Accordingly, with respect, I am of the view that the Federal Court Judge erred in his determination that the standard of review with respect to the interpretative issue is reasonableness and not correctness.

[60] Nonetheless, I recognize that the "[r]easonableness is the presumptive standard of review when a tribunal is interpreting its home statute or a statute closely connected to its function and with which it will have particular familiarity" (*Canadian Artists' Representation v. National Gallery of Canada*, 2014 SCC 42, [2014] 2 S.C.R. 197, at paragraph 13). Accordingly, I will also review the interpretative issue on the standard of reasonableness, in the event that I have erred in my identification of correctness as the applicable standard.

donc que le raisonnement appliqué par la Cour à l'occasion de l'affaire *Énergie atomique du Canada limitée* va d'autant dans le sens de ma décision de retenir la norme de la décision correcte relativement à la question d'interprétation.

[58] Dans l'arrêt *McLean c. Colombie-Britannique (Securities Commission)*, 2013 CSC 67, [2013] 3 R.C.S. 895, le juge Moldaver observe, au paragraphe 33 :

> Comme l'a maintes fois rappelé notre Cour depuis l'arrêt *Dunsmuir*, mieux vaut généralement laisser au décideur administratif le soin de clarifier le texte ambigu de sa loi constitutive. La raison en est que le choix d'une interprétation parmi plusieurs qui sont raisonnables tient souvent à des considérations de politique générale dont on présume que le législateur a voulu confier la prise en compte *au décideur administratif* plutôt qu'à une cour de justice. L'exercice de ce pouvoir discrétionnaire d'interprétation relève en effet de l'« expertise » du décideur administratif. [Non souligné dans l'original; italique dans l'original.]

[59] Il ressort de ce passage qu'il peut y avoir des cas où la norme de la décision correcte est appliquée à juste titre relativement à l'interprétation de la « loi constitutive » d'un tribunal administratif. Et, par les motifs que j'ai exposés, je conclus que tel est le cas en l'espèce. En conséquence, soit dit avec déférence, je suis d'avis que le juge de la Cour fédérale a commis une erreur lorsqu'il a conclu que la norme de contrôle applicable relativement à la question d'interprétation était celle de la décision raisonnable et non celle de la décision correcte.

[60] Néanmoins, je reconnais que la « norme de la décision raisonnable est présumée s'appliquer lorsqu'un tribunal administratif interprète sa loi constitutive ou une loi étroitement liée à son mandat et dont il a une connaissance approfondie » (*Front des artistes canadiens c. Musée des beaux-arts du Canada*, 2014 CSC 42, [2014] 2 R.C.S. 197, au paragraphe 13). En conséquence, j'examinerai aussi la question d'interprétation selon la norme de la décision raisonnable, dans l'éventualité où j'aurais commis une erreur en concluant que la norme de contrôle applicable était celle de la décision correcte.

B. What is the correct interpretation of the causal connection requirement of the phrase "arose out of or was directly connected with" in paragraph 21(2)(*a*) of the *Pension Act*?

[61] Having determined that the standard of review that must be applied to the interpretative issue is correctness, not reasonableness as found by the Federal Court Judge, I will "place myself into his shoes" and undertake a review of the issue of whether the Board's interpretation of the phrase "arose out of or was directly connected with" in paragraph 21(2)(*a*) of the *Pension Act* was correct.

[62] As noted above, the Board interpreted this phrase as requiring an applicant for a disability pension, pursuant to paragraph 21(2)(*a*) of the *Pension Act*, to establish that his or her military service was the primary cause of his or her claimed condition.

Position of the parties

[63] The appellant asserts that by virtue of this Court's decision in *Frye*, the level of causal connection mandated by the phrase "arose out of or was directly connected with" in paragraph 21(2)(*a*) of the *Pension Act* should be interpreted as requiring an applicant to establish only that his or her military service was among the contributing causes of the claimed condition in issue. As such, the appellant asserts that the Board's "primary cause" interpretation was incorrect.

[64] The respondent appeared to assert that the applicant's military service must be established to be the primary cause of such claimed condition, and accordingly, the Board made no interpretative error.

Federal Court jurisprudence

[65] There is disagreement at the Federal Court level, particularly since this Court's decision in *Frye*, as to

B. Quelle est l'interprétation correcte de l'exigence de causalité correspondant aux mots « consécutive ou rattachée directement [à] » à l'alinéa 21(2)*a*) de la *Loi sur les pensions*?

[61] Puisque j'ai conclu que la norme de contrôle qui doit être appliquée à la question d'interprétation est celle de la décision correcte, et non celle de la décision raisonnable comme l'avait conclu le juge de la Cour fédérale, je vais me « mettre à la place » de ce dernier et entreprendre l'examen de la question de savoir si l'interprétation que le Tribunal a faite des mots « consécutive ou rattachée directement [à] » à l'alinéa 21(2)*a*) de la *Loi sur les pensions* était correcte.

[62] Comme je l'ai signalé précédemment, le Tribunal a interprété ces mots comme exigeant que l'auteur de la demande de pension d'invalidité faite en vertu de l'alinéa 21(2)*a*) de la *Loi sur les pensions* établisse que son service militaire avait été la cause principale de son affection alléguée.

Les thèses des parties

[63] L'appelante affirme qu'en raison de la jurisprudence *Frye* de notre Cour, les mots « consécutive ou rattachée directement [à] » à l'alinéa 21(2)*a*) de la *Loi sur les pensions* doivent être interprétés comme exigeant seulement, en fait de degré de causalité, que le demandeur établisse que son service militaire a été une des causes contributives de l'affection alléguée dont il est question. Aussi, l'appelante soutient que l'interprétation du Tribunal aboutissant au critère de la « cause principale » est incorrecte.

[64] L'intimé semblait affirmer qu'il doit être établi que le service militaire de la personne qui présente la demande est la cause principale de l'affection alléguée, et que le Tribunal n'a donc commis aucune erreur d'interprétation.

La jurisprudence de la Cour fédérale

[65] Il y a désaccord au sein de la Cour fédérale, particulièrement depuis que la Cour a rendu l'arrêt *Frye*,

whether the primary cause level of causal connection is required by the phrase "arose out of or was directly connected with" in paragraph 21(2)(*a*) of the *Pension Act*. (See *John Doe v. Canada (Attorney General)*, 2004 FC 451, 249 F.T.R. 301; *Boisvert v. Canada (Attorney General)*, 2009 FC 735; and *Hall v. Canada (Attorney General)*, 2011 FC 1431.) And, because the Federal Court reviews decisions of the Board on this interpretative question, the divergence of views at the Federal Court level impacts upon decisions at the Board level.

Frye

[66] *Frye* is the only decision of this Court cited to us that provides an interpretation of the phrase "arose out of or was directly connected with". It will be useful then to consider the circumstances of that case.

[67] Ms. Frye was the spouse of Corporal Lee Arnold Berger, a career soldier who was deployed in firefighting activities that required him to be "on duty" 24 hours of the day. On the day of his death, he had been fighting fires for 16 hours. That evening, he died from injuries suffered as a result of being struck by a large vehicle as he was walking back to his camp from a late night swim at a nearby lake. Ms. Frye applied for a pension, pursuant to paragraph 21(2)(*b*) of the *Pension Act*, on the basis that her husband's death resulted from a fatal injury that "arose out of or was directly connected with" his military service.

[68] The Board interpreted the phrase "arose out of or was directly connected with" as requiring the establishment of a direct or immediate causal connection between Corporal Berger's fatal injury and his military service. It concluded that his fatal injury was directly caused by the truck that struck him and that his recreational activities were not part of his military service.

[69] On judicial review, the Federal Court Judge agreed with the Board's interpretation of the phrase "arose out of or was directly connected with" but held,

quant à savoir si les mots « consécutive ou rattachée directement [à] » à l'alinéa 21(2)*a*) de la *Loi sur les pensions* exigent un degré de causalité correspondant au critère de la « cause principale » (voir *John Doe c. Canada (Procureur général)*, 2004 CF 451; *Boisvert c. Canada (Procureur général)*, 2009 CF 735; et *Hall c. Canada (Procureur général)*, 2011 CF 1431). Et, puisque la Cour fédérale examine les décisions du Tribunal relativement à cette question d'interprétation, la divergence d'opinions au sein de la Cour fédérale a des répercussions sur des décisions du Tribunal.

L'arrêt Frye

[66] L'arrêt *Frye* est le seul arrêt de la Cour qu'on nous a cité qui donne une interprétation des mots « consécuti[ve] ou rattaché[e] directement à ». Il est donc utile d'examiner les faits de cette affaire.

[67] M^me^ Frye était l'épouse du caporal Lee Arnold Berger, militaire de carrière, qui était déployé dans le cadre d'activités de lutte contre les incendies, ce qui l'obligeait à être [TRADUCTION] « de service » 24 heures par jour. Le jour de son décès, il avait combattu des feux pendant 16 heures. Ce soir-là, il est décédé des suites de blessures subies lorsqu'il a été frappé par un gros véhicule alors qu'il revenait à pied à son camp à la suite d'une baignade nocturne dans un lac situé non loin du camp. M^me^ Frye a demandé une pension, en vertu de l'alinéa 21(2)*b*) de la *Loi sur les pensions*, au motif que le décès de son époux résultait d'une blessure mortelle « consécutive ou rattachée directement [à] » son service militaire.

[68] Le Tribunal a interprété les mots « consécuti[ve] ou rattaché[e] directement à » comme exigeant l'établissement d'une causalité directe ou immédiate entre la blessure mortelle du caporal Berger et son service militaire. Il a conclu que la blessure mortelle du caporal Berger avait été causée directement par le camion qui l'avait frappé et que ses activités récréatives ne faisaient pas partie de son service militaire.

[69] Aux termes de la procédure en contrôle judiciaire, le juge de la Cour fédérale a retenu l'interprétation que le Tribunal avait faite des mots « consécuti[ve] ou

on a factual basis, that Corporal Berger's fatal injury was directly connected with his military service.

[70] This Court disagreed with the interpretation of the phrase "arose out of or was directly connected with" that was given by the Board and the Federal Court Judge. The Court found that the phrase encompassed two distinct *types* of causal connection, either of which, if established, would satisfy the required causal connection between the decedent's fatal injury and his or her military service.

[71] The Court agreed that the *type* of connection contemplated by the phrase "directly connected with" was a direct factual connection between the fatal injury and the decedent's military service. In the circumstances, being struck by the truck was the direct factual cause of Corporal Berger's fatal injury and that unfortunate event was not directly connected with his military service. As such, the Court agreed with the Board that the "directly connected with" element was not satisfied.

[72] The Court went on to conclude that a different *type* of causal connection between the fatal injury and the decedent's military service was contemplated by the phrase "arose out of". In other words, some kind of connection other than a direct or immediate one would be sufficient. While the Court did not offer a specific formulation of this *type* of acceptable non-direct causal connection, it did state that an acceptable causal connection would not extend so far as to include a mere temporal connection, such as simply serving in the armed forces at the time of the fatal injury.

[73] The Court went on to conclude that Corporal Berger's recreational swimming was, in some fashion, mandated by a military policy that required him to be relaxed, rested and fit for his continuing firefighting duties. As such, it followed that his engagement in this form of militarily-mandated recreational activity was a part of his military service. Thus, while this activity could not be said to have had a direct causal connection with Corporal Berger's fatal injury (which was directly caused by the truck), the Court nonetheless found that this activity had a non-direct causal connection with his

rattaché[e] directement à », mais il a conclu, compte tenu des faits, que la blessure fatale du caporal Berger était rattachée directement à son service militaire.

[70] Notre Cour a rejeté l'interprétation que le Tribunal et le juge de la Cour fédérale avaient donnée aux mots « consécuti[ve] ou rattaché[e] directement à ». Elle a conclu que l'expression visait deux types distincts de causalité, et que l'établissement de l'une ou de l'autre répondait à l'exigence de causalité entre la blessure mortelle du défunt et son service militaire.

[71] La Cour a retenu l'idée que le type de rattachement envisagé par les mots « rattachée directement à » était celui du lien direct entre la blessure mortelle et le service militaire du défunt. Dans les circonstances, le fait d'avoir été frappé par le camion constituait la cause directe de la blessure mortelle du caporal Berger, et cet événement malheureux n'était pas rattaché directement à son service militaire. Aussi, la Cour a convenu avec le Tribunal qu'il n'avait pas été satisfait au critère correspondant aux mots « rattachée directement à ».

[72] La Cour a ensuite conclu que les mots « consécutive à » évoquaient un type différent de causalité entre la blessure mortelle et le service militaire du défunt. Autrement dit, une certaine sorte de lien autre que direct ou immédiat serait suffisant. La Cour n'a pas proposé de formulation précise de ce type de causalité non directe acceptable, mais elle a observé qu'une causalité acceptable n'irait pas jusqu'à inclure un simple lien temporel, comme le simple fait d'être au service des forces armées au moment de la blessure mortelle.

[73] La Cour a ensuite conclu que la nage récréative du caporal Berger était, d'une certaine façon, requise par une politique militaire qui exigeait que le caporal Berger soit détendu, reposé et apte à reprendre ses activités de lutte contre les incendies. Il s'ensuivait donc que la participation du caporal Berger à cette forme d'activité récréative répondant à une exigence militaire faisait partie de son service militaire. Aussi, bien que cette activité ne puisse pas être considérée comme ayant eu une causalité directe avec la blessure mortelle du caporal Berger (qui avait été causée directement par le camion),

fatal injuries that was sufficient for the Court to conclude that those injuries "arose out of" his military service. In other words, Corporal Berger's militarily-mandated swimming activities were the non-direct cause of his fatal injuries.

[74] In my view, *Frye* stands for the proposition that the causal connection between a fatal injury and the decedent's military service that is required by the phrase "arose out of" in paragraph 21(2)(*b*) of the *Pension Act* can be satisfied by a non-direct causal connection.

Frye *is distinguishable*

[75] The decision in *Frye* teaches that the causal connection requirements of the phrase "arose out of or was directly connected with" can be satisfied by either of the two *types*: a direct causal connection or a non-direct causal connection. In reaching its decision, in my view, the Court found that Corporal Berger's militarily-mandated recreational swimming activities were the non-direct cause of his fatal injury, and therefore his fatal injury "arose out of" his military service.

[76] In the instant circumstances, the record establishes that both the military factors and the personal factors have a direct causal connection with Ms. Cole's claimed condition. Thus, unlike *Frye*, which dealt with a single non-direct causal connection between the fatal injury and the decedent's military service, the issue in this case relates to the interpretation of "directly connected with" in circumstances involving *two* sets of distinct and directly connected causal factors.

Direct connection but multiple causes

[77] It must be recalled that an applicant for a disability pension, pursuant to paragraph 21(2)(*a*) of the *Pension Act*, is required to establish that the claimed condition was causally connected to the applicant's military service.

la Cour a néanmoins conclu que cette activité avait une causalité indirecte avec ses blessures mortelles qui était suffisante pour que la Cour conclue que ces blessures étaient « consécutives à » son service militaire. Autrement dit, les activités de natation du caporal Berger répondant à une exigence militaire avaient été la cause indirecte de ses blessures mortelles.

[74] À mon avis, la jurisprudence *Frye* enseigne qu'une causalité indirecte entre une blessure mortelle et le service militaire du défunt peut satisfaire à l'exigence de causalité qui correspond aux mots « consécutive [à] » à l'alinéa 21(2)*b*) de la *Loi sur les pensions*.

L'affaire Frye *peut être distinguée de la présente affaire*

[75] La jurisprudence *Frye* enseigne qu'il y a deux types de causalité qui peuvent satisfaire aux exigences de causalité correspondant aux mots « consécuti[ve] ou rattaché[e] directement à » : la causalité directe ou la causalité indirecte. Pour parvenir à sa décision, à mon avis, la Cour a conclu que les activités de natation du caporal Berger répondant à une exigence militaire avaient été la cause indirecte de sa blessure mortelle, et sa blessure mortelle avait donc été « consécutive à » son service militaire.

[76] Dans la présente affaire, il ressort du dossier que les facteurs militaires et les facteurs personnels ont une causalité directe avec l'affection alléguée de M^me^ Cole. Ainsi, à la différence de l'affaire *Frye*, où il était question d'un seul lien de causalité indirect entre la blessure mortelle et le service militaire du défunt, la question en litige en l'espèce tient à l'interprétation des mots « rattaché[e] directement à » dans un contexte où il y a deux ensembles de facteurs causaux distincts et rattachés directement.

Lien direct, mais causes multiples

[77] Il faut rappeler que le demandeur d'une pension d'invalidité en vertu de l'alinéa 21(2)*a*) de la *Loi sur les pensions* est tenu d'établir l'existence d'un lien de causalité entre son service militaire et l'affection alléguée.

[78] Thus, where the claimed condition is traceable to two direct causes, the interpretative issue is whether the phrase "directly connected with" requires the applicant to establish that his or her military service is the primary cause of that condition. In the circumstances of this appeal, the issue is whether Ms. Cole must establish that the military factors played a larger role in bringing about her major depression than the personal factors.

[79] In the present circumstances, this interpretation simply asks whether the military factors have a larger causal connection to the claimed condition than the personal factors. If the answer is affirmative, then the direct causal connection is established. If the answer is negative, then such connection is not established.

[80] Asked another way, in the circumstances of this appeal, in which both the military factors and the personal factors have a direct causal connection with the claimed condition, the question is whether the causal connection requirement in the phrase "directly connected with" can *only* be satisfied if the military factors are the larger of those two causes. In my view, the answer to this question is no. Consequently, I am of the view that the primary cause interpretation of the causal connection requirement in the phrase "directly connected with" is incorrect.

Textual, contextual and purposive interpretative analysis

[81] Issues of statutory interpretation regularly arise in income tax cases. In *Mathew v. Canada*, 2005 SCC 55, [2005] 2 S.C.R. 643, the Supreme Court, at paragraphs 42 and 43, provided the following guidance with respect to statutory interpretation:

There is an abiding principle of interpretation: to determine the intention of the legislator by considering the text, context and purpose of the provisions at issue. This applies to the Income Tax Act and the GAAR as much as to any other legislation.

[78] Aussi, lorsque l'affection alléguée peut être rattachée à deux causes directes, la question d'interprétation est celle de savoir si les mots « rattachée directement [à] » exigent que le demandeur établisse que son service militaire est la cause principale de cette affection. Dans les circonstances du présent appel, la question qui se pose est celle de savoir si M^me^ Cole doit établir que les facteurs militaires ont joué un rôle plus important que les facteurs personnels dans le développement de sa dépression majeure.

[79] Dans les présentes circonstances, il faut simplement rechercher si les facteurs militaires ont une causalité plus importante avec l'affection alléguée que les facteurs personnels. Si la réponse est affirmative, alors le lien de causalité direct a été établi. Si la réponse est négative, alors un tel lien n'est pas établi.

[80] Posée différemment, dans les circonstances du présent appel, où l'ensemble de facteurs militaires et l'ensemble de facteurs personnels présentent tous deux une causalité directe avec l'affection alléguée, la question est celle de savoir s'il peut être satisfait à l'exigence de causalité correspondant aux mots « rattachée directement [à] » seulement si l'ensemble de facteurs militaires constitue la plus importante de ces deux causes. À mon avis, la réponse à cette question est négative. Par conséquent, je suis d'avis que l'interprétation de l'exigence de causalité correspondant aux mots « rattachée directement [à] » qui conduit au critère de la cause principale est incorrecte.

Analyse interprétative textuelle, contextuelle et téléologique

[81] Les affaires d'impôt sur le revenu soulèvent régulièrement des questions d'interprétation des lois. À l'occasion de l'affaire *Mathew c. Canada*, 2005 CSC 55, [2005] 2 R.C.S. 643, aux paragraphes 42 et 43, la Cour suprême a donné les orientations suivantes concernant l'interprétation des lois :

Il existe un principe d'interprétation constant : il faut dégager l'intention du législateur en tenant compte du libellé, du contexte et de l'objet des dispositions en cause. Ce principe s'applique autant à la Loi de l'impôt sur le revenu et à la RGAÉ qu'à toute autre mesure législative.

We add this. While it is useful to consider the three elements of statutory interpretation separately to ensure each has received its due, they inevitably intertwine. For example, statutory context involves consideration of the purposes and policy of the provisions examined. And while factors indicating legislative purpose are usefully examined individually, legislative purpose is at the same time the ultimate issue — what the legislator intended. [Emphasis added.]

Textual consideration

[82] The text of the phrase "directly connected with" in paragraph 21(2)(*a*) of the *Pension Act* clearly requires a causal relationship of a factual nature between the applicant's military service and his or her claimed condition. However, it does not stipulate any level or degree of causation. Accordingly, a textual analysis does not, in and of itself, validate the primary cause interpretation of this phrase.

Contextual consideration

[83] Both subsections 21(1) and (2) of the *Pension Act* permit awards of pensions in respect of deaths, injuries or diseases that arise out of or are directly connected with military service.

[84] As previously noted, paragraphs 21(1)(*a*) and (*b*) of the *Pension Act* apply in respect of wartime or special duty service and embody the so-called insurance principle referred to above. In that regard, some level of causal or temporal connection is required between the affliction and the military service to establish pension entitlement.

[85] In contrast, paragraphs 21(2)(*a*) and (*b*) of the *Pension Act* apply to afflictions arising in peace time military service in respect of which something less than the full insurance principle applies. In those circumstances, a higher degree of causal nexus between the affliction and the military service is required to establish pension entitlement.

Nous tenons à ajouter que, bien qu'il soit utile d'examiner séparément les trois éléments d'interprétation législative de manière à ce que chacun reçoive l'attention qu'il mérite, force est de constater que ces éléments sont inextricablement liés. Par exemple, en analysant le contexte législatif, il faut tenir compte des objets et de la politique générale des dispositions examinées. Et bien qu'il soit utile d'examiner individuellement les facteurs indiquant un objectif législatif, cet objectif législatif représente en même temps la question à laquelle il faut répondre en définitive, à savoir ce qu'a voulu le législateur. [Non souligné dans l'original.]

Examen textuel

[82] Les mots « rattachée directement [à] » à l'alinéa 21(2)*a*) de la *Loi sur les pensions* exigent clairement un lien de causalité concret entre le service militaire du demandeur et son affection alléguée. Toutefois, ces mots n'évoquent aucun niveau ou degré de causalité en particulier. En conséquence, l'analyse textuelle ne valide pas, en elle-même, l'interprétation de ces mots qui conduit au critère de la cause principale.

Examen contextuel

[83] Selon les paragraphes 21(1) et (2) de la *Loi sur les pensions*, le juge peut accorder une pension à l'égard des décès, des blessures ou des maladies qui sont consécutifs ou rattachés directement au service militaire.

[84] Comme je l'ai signalé précédemment, les alinéas 21(1)*a*) et *b*) de la *Loi sur les pensions* joue relativement au service en temps de guerre ou au service spécial, et ils donnent corps au « principe de l'assurance » signalé précédemment. À cet égard, un certain lien de causalité ou de lien temporel est requis entre l'affection et le service militaire pour que soit établi un droit à pension.

[85] Par contre, entrent dans les prévisions des alinéas 21(2)*a*) et *b*) de la *Loi sur les pensions* les affections qui se manifestent durant le service militaire en temps de paix, lesquels ne suivent pas pleinement le principe de l'assurance. Dans ces circonstances, un degré plus élevé de causalité entre l'affection et le service militaire est requis pour établir un droit à pension.

[86] Thus, it may be reasonably concluded that contextually considered, the phrase "directly connected with" is intended to require a higher degree of causal connection between the claimed condition and peace time military service than that required under subsection 21(1) of the *Pension Act*. However, that contextual comparison does not establish that the primary cause level of causation is necessarily mandated.

Purposive consideration

[87] In many instances, courts are presented with limited guidance when attempting to ascertain Parliament's purpose in enacting a particular piece of legislation. However, in the present circumstances, the Court is specifically instructed, by section 2 of that Act and section 3 of the VRAB Act, as to how the Board and any reviewing court must interpret the provisions of the *Pension Act*.

[88] In my view, these provisions mandate an interpretation of the level of causal connection that is required by the phrase "directly connected with" that will facilitate, rather than impede, the awarding of pensions to members of the armed forces who have been disabled or have died as a result of military service.

[89] The primary cause, and the "but for" test referred to by the Federal Court Judge in paragraph 29 of his reasons, may well be consistent with the level of factual causation that is commonly applied in tort cases. However, adopting that ordinary civil standard of causation, in my view, is inconsistent with the parliamentary admonishments in section 2 of the *Pension Act* and section 3 of the VRAB Act.

[90] In my view, a lower level of causal connection than the "but for" test is required by the phrase "directly connected with" in paragraph 21(2)(*a*) of the *Pension Act*. Otherwise, these liberal interpretative admonishments would have no meaning in the circumstances

[86] Ainsi, l'on peut raisonnablement conclure que, d'après l'examen contextuel, les mots « rattachée directement [à] » sont censés exiger un degré plus élevé de causalité entre l'affection alléguée et le service militaire en temps de paix que ce qu'exige le paragraphe 21(1) de la *Loi sur les pensions*. Toutefois, cette comparaison contextuelle n'établit pas que le niveau de causalité requis est nécessairement celui de la cause principale.

Examen téléologique

[87] Dans bien des cas, les juges judiciaires ont peu de repères lorsqu'ils tentent de cerner l'intention qui animait le législateur au moment de promulguer un texte législatif donné. Toutefois, en l'espèce, des instructions précises sont données à la Cour par l'article 2 de la *Loi sur les pensions* et par l'article 3 de la Loi sur le TACRA, sur la manière dont le Tribunal et toute cour réformatrice doivent interpréter les dispositions de la *Loi sur les pensions*.

[88] À mon avis, ces dispositions appellent une interprétation du degré de causalité exigé par les mots « rattachée directement [à] » qui élargit, au lieu de restreindre, le droit à une pension des membres des forces armées qui sont devenus invalides ou qui sont décédés par suite de leur service militaire.

[89] Le critère de la cause principale, et le critère du facteur déterminant (aussi désigné par l'expression « n'eût été ») évoqué par le juge de la Cour fédérale au paragraphe 29 de ses motifs, correspondent peut-être bien au degré de causalité qui est généralement appliqué dans les affaires de responsabilité civile délictuelle. Toutefois, l'adoption de cette norme civile ordinaire en ce qui a trait à la causalité me paraît incompatible avec les directives que le législateur nous donne à l'article 2 de la *Loi sur les pensions* et à l'article 3 de la Loi sur le TACRA.

[90] À mon avis, les mots « rattachée directement [à] » à l'alinéa 21(2)*a*) de la *Loi sur les pensions* exigent un degré de causalité inférieur à celui du critère du facteur déterminant. Autrement, l'appel à une interprétation libérale n'auraient aucun sens dans les circonstances de

under consideration. It follows, in my view, that an interpretation of the phrase "directly connected with" that requires that a pension applicant's military service was the primary cause of his or her claimed condition is not only incorrect, but also unreasonable. The following example is illustrative of both the incorrectness and the unreasonableness of the primary cause interpretation.

[91] While recognizing that a condition such as major depression is complex and its causes are difficult to assess, much less with mathematical precision, if Ms. Cole's personal factors were determined to have been 51 percent responsible for her major depression, it would follow that her military factors must have been 49 percent responsible. Thus, the "primary cause" of her claimed condition would not be her military service and her application would be dismissed.

[92] In my view, this result cannot be consistent with the purpose of the *Pension Act*, which is to ensure that our country honours its obligations to the women and men who serve in our armed forces and who have suffered injury, disease or death as a result.

What degree of causation is required to establish a direct causal connection?

[93] At the hearing, counsel for Ms. Cole asserted that any level or degree of causal connection between her claimed condition and her military service would be sufficient. Thus, we were urged to accept that if it could be shown that the military factors were 1 percent responsible for that claimed condition, a sufficient causal connection to ground pension entitlement would exist.

[94] In my view, such a minor degree of causal connection between a claimed condition and an applicant's military service will not be sufficient.

[95] So, what level of causal connection greater than a mere possibility but less than the primary cause will be sufficient, having regard to the purpose that the *Pension Act* is intended to achieve?

l'espèce. Il s'ensuit, à mon avis, que l'interprétation des mots « rattachée directement [à] » qui exige que le service militaire d'un demandeur de pension ait été la cause principale de son affection alléguée est non seulement incorrecte, mais aussi déraisonnable. L'exemple suivant illustre à la fois qu'est incorrect et déraisonnable l'interprétation prônant le critère de la cause principale.

[91] Tout en reconnaissant qu'une affection comme une dépression majeure est complexe et que ses causes sont difficiles à apprécier — il n'est surtout pas question de précision mathématique — si l'on devait conclure que les facteurs personnels de M^me^ Cole avaient contribué à 51 p. 100 de sa dépression majeure, il s'ensuivrait que ses facteurs militaires auraient dû y contribuer à 49 p. 100. Ainsi, la « cause principale » de son affection alléguée ne serait pas son service militaire, et sa demande serait rejetée.

[92] À mon avis, cette solution ne peut pas être considérée comme compatible avec l'objet de la *Loi sur les pensions*, qui est d'assurer que notre pays honore ses obligations envers les femmes et les hommes qui ont servi au sein de nos forces armées et qui ont subi une blessure ou contracté une maladie ou sont décédés par suite de ce service.

Quel degré de causalité est exigé pour établir une causalité directe?

[93] À l'audience, l'avocat de M^me^ Cole a affirmé que n'importe quel niveau ou degré de causalité entre l'affection alléguée de M^me^ Cole et son service militaire serait suffisant. Ainsi, on nous a exhortés à admettre que s'il pouvait être démontré que les facteurs militaires avaient contribué à 1 p. 100 de cette affection alléguée, il existerait une causalité suffisante pour établir un droit à pension.

[94] À mon avis, un degré aussi faible de causalité entre une affection alléguée et le service militaire d'un demandeur ne serait pas suffisant.

[95] Dans ce cas, quel degré de causalité supérieur à une simple possibilité, mais inférieur à la cause principale serait suffisant, eu égard à l'objet que la *Loi sur les pensions* est censée réaliser?

[96] In paragraph 35 of his reasons, the Federal Court Judge stated:

> It seems to me that the words "arising out of" and the overall context of the statute call for something more than some nexus or causal connection, and require that military service be the main or prevalent cause of the disease or injury, or at the very least a significant factor. Another way of putting it might be to say the injury or disease would not have occurred but for [emphasis added by de Montigny J.] the military service. [Emphasis added.]

The underlined portion of this passage indicates that the Federal Court Judge at least countenanced an interpretation in which the requisite level of causal connection might be lower than primary cause.

Significant factor

[97] Recognizing that there is no determinative authority on this issue and being mindful of the admonishments in section 2 of the *Pension Act* and section 3 of the VRAB Act that the provisions of the *Pension Act* are to be liberally construed and interpreted, I conclude that, for the purposes of establishing entitlement to a disability pension under paragraph 21(2)(*a*) of the *Pension Act* on the basis that the claimed condition was "directly connected with" the applicant's military service, the applicant must establish only a significant causal connection between the applicant's claimed condition and his or her military service. In other words, a causal connection that is significant but less than primary will be sufficient. Thus, an applicant's military service will provide a sufficient causal connection with his or her claimed condition, such that the claimed condition is "directly connected with" such military service, where he or she establishes that his or her military service was a significant factor in bringing about that claimed condition.

[98] Reverting to my earlier hypothetical, if military factors could somehow be demonstrated to have been 49 percent responsible for Ms. Cole's claimed condition, in my view, those factors would clearly constitute a significant causal connection between her claimed condition and her military service that would be sufficient to establish the level of causal connection required

[96] Au paragraphe 35 de ses motifs, le juge de la Cour fédérale a observé :

> Il me semble, que le terme « consécutive » et le contexte général de la loi exigent qu'il soit démontré davantage qu'un certain lien ou rapport causal, et que le service militaire doit être la cause principale ou prédominante de la maladie ou de la blessure, ou à tout le moins avoir joué un rôle significatif. On pourrait sans doute tout aussi bien dire qu'il doit être établi que la blessure ou la maladie ne serait pas survenue n'eût été [soulignement ajouté par le juge de Montigny] le service militaire. [Non souligné dans l'original.]

Il ressort de la partie soulignée de ce passage que le juge de la Cour fédérale a à tout le moins envisagé une interprétation suivant laquelle le degré requis de causalité pourrait être inférieur à celui de la cause principale.

Facteur important

[97] Je conclus, en reconnaissant qu'il n'y a aucune jurisprudence déterminante sur cette question, et en ayant à l'esprit les directives énoncées à l'article 2 de la *Loi sur les pensions* et à l'article 3 de la Loi sur le TACRA selon lesquelles les dispositions de la *Loi sur les pensions* doivent s'interpréter de façon libérale, que, pour établir le droit à une pension d'invalidité en vertu de l'alinéa 21(2)*a*) de la *Loi sur les pensions* au motif que l'affection alléguée était « rattachée directement au » service militaire du demandeur, le demandeur doit seulement établir une causalité importante entre son affection alléguée et son service militaire. Autrement dit, une causalité qui est importante, mais moins que principale, sera suffisante. Ainsi, le service militaire du demandeur présentera une causalité suffisante avec son affection alléguée pour que l'on puisse considérer que celle-ci est « rattachée directement [à] » ce service militaire lorsque le demandeur établit que son service militaire a été un facteur important dans le déclenchement de l'affection alléguée.

[98] Pour revenir à l'hypothèse que j'ai formulée précédemment, si l'on pouvait démontrer que les facteurs militaires avaient contribué à 49 p. 100 de l'affection alléguée de M^me^ Cole, ces facteurs constitueraient clairement, à mon avis, une causalité importante entre son affection alléguée et son service militaire, laquelle serait suffisante pour répondre au degré exigé par les mots

by the phrase "directly connected with" in paragraph 21(2)(*a*) of the *Pension Act*. That said, I am not suggesting that a percentage close to 49 percent will be required to establish a significant causal connection between the claimed condition and the applicant's military service. Indeed, attempting to quantify levels of factual causation with mathematical precision borders on the theoretical.

[99] The existence of a significant causal connection in the context of an application for a disability pension under paragraph 21(2)(*a*) of the *Pension Act* will be a question of fact. Those with expertise in fact-finding, in my view, will no doubt be able to recognize a significant factor when they see one. Indeed, it may be possible to identify a significant causal connection as simply one that is not insignificant. Moreover, it is not at all clear to me that it will be meaningfully more difficult for fact-finders with expertise to determine the existence of a significant causative factor than it has been for them to determine the existence of the primary causal factor.

C. Was the Board's primary cause interpretation of the causal connection requirement of the phrase "arose out of or was directly connected with" in paragraph 21(2)(*a*) of the *Pension Act* unreasonable?

[100] As indicated above, it is my view that the interpretative issue is to be reviewed on the standard of correctness and I have done so.

[101] In the event that I am incorrect and the standard of review is reasonableness, I am of the view that the Board's primary cause interpretation of the causal connection requirement in the phrase "directly connected with", in paragraph 21(2)(*a*) of the *Pension Act*, is unreasonable.

[102] The Board and the Federal Court Judge undertook no analysis to support the conclusion that the causal connection requirement of the phrase "directly connected with" was the primary cause. At the Federal Court level,

« rattachée directement [à] » à l'alinéa 21(2)*a*) de la *Loi sur les pensions*. Cela dit, je ne dis pas qu'un pourcentage de près de 49 p. 100 sera nécessaire pour établir une causalité importante entre l'affection alléguée et le service militaire du demandeur. D'ailleurs, il n'est pas très réaliste de tenter de quantifier des degrés de causalité factuelle avec une précision mathématique.

[99] L'existence d'une causalité importante en matière de demande de pension d'invalidité aux termes de l'alinéa 21(2)*a*) de la *Loi sur les pensions* est une question de fait. À mon avis, ceux qui possèdent des compétences spécialisées en matière de recherche des faits sauront certainement reconnaître un facteur important lorsqu'ils le constateront. De fait, il serait possible de reconnaître un rapport causal important tout simplement comme celui qui n'est pas négligeable. En outre, je ne suis pas du tout certain qu'il est sensiblement plus difficile pour les personnes compétentes chargées d'enquêter sur les faits de déterminer l'existence d'un facteur causal important qu'il ne l'a été pour eux de déterminer l'existence du facteur causal principal.

C. L'interprétation par le Tribunal de l'expression « consécutive ou rattachée directement [à] » à l'alinéa 21(2)*a*) de la *Loi sur les pensions* comme exigeant une causalité correspondant au critère de la cause principale était-elle déraisonnable?

[100] Comme je l'ai signalé précédemment, je suis d'avis que la question d'interprétation doit être contrôlée selon la norme de la décision correcte, et c'est ce que j'ai fait.

[101] Dans l'éventualité où j'aurais commis une erreur et que la norme de contrôle soit celle de la décision raisonnable, je suis d'avis que l'interprétation par le Tribunal des mots « rattachée directement [à] » à l'alinéa 21(2)*a*) comme exigeant une causalité correspondant au critère de la cause principale est déraisonnable.

[102] Le Tribunal et le juge de la Cour fédérale n'ont entrepris aucune analyse au soutien de leur conclusion selon laquelle les mots « rattachée directement [à] » exigeaient une causalité correspondant au critère de la

the Federal Court Judge referred to his prior decision in *Boisvert* as having decided the question.

[103] In *McLean*, Justice Moldaver teaches that when questions of statutory interpretation are reviewed on a standard of reasonableness, the Court must show deference to and accept *any* reasonable interpretation of the provision adopted by the administrative decision maker, even if *other* reasonable interpretations exist.

[104] Thus, the question is whether the Board's primary cause interpretation is reasonable. With respect, in my view, it is not.

[105] In answering this question, *McLean* informs that the provision in issue must be construed using the textual, contextual and purposive analysis that is required in any exercise of statutory interpretation. Thus, in this case, the Board's primary cause interpretation will stand unless it is shown to be unreasonable, on the basis of such analysis.

Textual consideration

[106] As indicated previously, the phrase "directly connected with" contemplates a causal connection between the applicant's military service and his or her claimed condition. However, that phrase does not stipulate any particular degree of causal connection. As such, a textual analysis of that phrase does not establish that the primary cause test is unreasonable.

Contextual consideration

[107] The contextual consideration of this phrase that appears in paragraph 86 of these reasons, shows that Parliament intended to establish a higher level of causal connection requirement for subsection 21(2) pensions than for subsection 21(1) pensions. However, this contextual comparison does not signify any particular degree of causal connection for the phrase "directly connected

cause principale. À la Cour fédérale, le juge a conclu que la question avait été tranchée par sa propre jurisprudence *Boisvert*, qu'il avait lui-même rendue.

[103] Par l'arrêt *McLean*, le juge Moldaver enseigne que, lorsque des questions d'interprétation des lois sont examinées selon la norme de la raisonnabilité, la Cour doit faire preuve de retenue à l'égard de toute interprétation raisonnable de la disposition adoptée par le décideur administratif, et elle doit confirmer cette interprétation, et ce, même s'il existe d'autres interprétations raisonnables.

[104] Ainsi, la question est celle de savoir si l'interprétation du Tribunal qui aboutit au critère de la cause principale est raisonnable. Je conclus, avec égards, que tel n'est pas le cas.

[105] Pour répondre à cette question, la jurisprudence *McLean* enseigne que la disposition en cause doit être interprétée au moyen de l'analyse textuelle, contextuelle et téléologique qui est prescrite s'impose lorsqu'il faut interpréter une loi. Aussi, en l'espèce, l'interprétation du Tribunal qui aboutit au critère de la cause principale sera retenue, à moins qu'il ne soit démontré qu'elle est déraisonnable, selon l'analyse susmentionnée.

Examen textuel

[106] Comme je l'ai mentionné précédemment, les mots « rattachée directement [à] » évoquent une causalité entre le service militaire du demandeur et son affection alléguée. Toutefois, ces mots n'évoquent aucun degré précis de causalité. Ainsi, l'analyse textuelle de ces mots n'établit pas que le critère de la cause principale est déraisonnable.

Examen contextuel

[107] Il ressort de l'examen contextuel de ces mots qui apparaît au paragraphe 86 des présents motifs que le législateur entendait exiger un degré de causalité plus élevé pour les pensions visées au paragraphe 21(2) que pour les pensions visées au paragraphe 21(1). Toutefois, cette comparaison contextuelle ne fait ressortir aucun degré de causalité précis à l'égard des mots « rattachée

with". As such, a contextual consideration of this phrase does not establish that the primary cause test is unreasonable.

Purposive consideration

[108] As set forth above, Parliament has mandated that a liberal interpretation of the *Pension Act* must be given with a view to ensuring that our country's obligation to members of the armed forces who have been disabled or have died as a result of military service may be fulfilled. In my view, this means that a lower level of causal connection than the ordinary civil standard of the "but for" test was intended by Parliament when it enacted the phrase "directly connected with". It follows, in my view, that in adhering to the primary cause level of causation, the Board unreasonably interpreted the phrase "directly connected with".

[109] My somewhat theoretical example in paragraph 91 of these reasons is a further illustration of the unreasonableness of the primary cause test. This is especially so in circumstances—such as those under consideration in this appeal—involving illnesses, the causes of which are difficult to diagnose with the degree of precision necessary to establish a primary cause.

[110] The significant cause level of causation that I have endorsed provides a flexible approach to the establishment of the requisite causal connection between military service and a claimed condition and is, in my view, fully consistent with the liberal interpretation admonishments contained in section 2 of the *Pension Act* and section 3 of the VRAB Act. This flexibility favourably distinguishes the significant cause interpretation from the primary cause interpretation.

[111] Accordingly, for these reasons, I am of the view that an interpretation of the phrase "directly connected with" in paragraph 21(2)(*a*) of the *Pension Act* that requires an applicant to establish that his or her military service is the primary cause of his or her claimed condition is unreasonable, and a decision to deny the award

directement [à] ». Ainsi, il ne ressort pas de l'examen contextuel de ces mots que le critère de la cause principale est déraisonnable.

Examen téléologique

[108] Comme il a été exposé précédemment, le législateur exige que la *Loi sur les pensions* soit interprétée de façon libérale, afin d'assurer que notre pays honore ses obligations envers les membres des forces armées qui sont devenus invalides ou sont décédés par suite de leur service militaire. À mon avis, il s'ensuit que le législateur envisageait un degré de causalité inférieur à celui de la norme civile ordinaire du critère du facteur déterminant lorsqu'il a promulgué les mots « rattachée directement [à] ». Il s'ensuit, à mon avis, qu'en retenant le degré de causalité correspondant au critère de la cause principale, le Tribunal a interprété de manière déraisonnable les mots « rattachée directement [à] ».

[109] Mon exemple quelque peu théorique au paragraphe 91 des présents motifs illustre également le caractère déraisonnable du critère de la cause principale. Cela est particulièrement vrai dans des situations — comme celle dont il est question en l'espèce — relatives à des maladies dont les causes sont difficiles à cerner avec le degré de précision nécessaire pour établir une cause principale.

[110] Le degré de causalité de la cause importante que j'ai retenu permet une approche souple à l'égard de l'établissement de la causalité requise entre le service militaire et une affection alléguée, et, à mon avis, s'accorde parfaitement avec les exigences d'une interprétation libérale énoncées à l'article 2 de la *Loi sur les pensions* et à l'article 3 de la Loi sur le TACRA. Cette souplesse démarque favorablement l'interprétation conduisant au critère de la cause importante de l'interprétation conduisant au critère de la cause principale.

[111] En conséquence, par ces motifs, je suis d'avis que l'interprétation des mots « rattachée directement [à] » à l'alinéa 21(2)*a*) de la *Loi sur les pensions* qui exige qu'un demandeur établisse que son service militaire est la cause principale de son affection alléguée est déraisonnable, ainsi qu'une décision de refuser une

of a pension on the basis of such an interpretation is not within the range of reasonable outcomes of the decision-making process under consideration.

D. Did the Board err with respect to the application of evidence issue?

[112] Having concluded that the Board erred in its selection of the primary cause test to determine whether Ms. Cole's claimed condition was sufficiently causally connected to her military service, it is clear that the Board's decision to deny her application for a disability pension cannot stand.

DISPOSITION

[113] For the foregoing reasons, I would allow the appeal, set aside the judgment of the Federal Court Judge, dated March 31, 2014 and return the matter to the Board for re-determination in accordance with these reasons, with costs in the appeal and in the Federal Court.

WEBB J.A.: I agree.

***

The following are the reasons for judgment rendered in English by

[114] GAUTHIER J.A. (concurring reasons): I agree with my colleague Ryer J.A. that this appeal should be allowed and the matter returned to the Board for re-determination. However, I wish to comment briefly on some issues.

[115] With respect to the standard of review, I respectfully disagree that correctness is the standard to be applied to the Board's interpretation of paragraph 21(2)(*a*) of the *Pension Act*. As my colleague acknowledges, the Supreme Court has stated that reasonableness is the presumptive standard of review where a tribunal is interpreting its home statute or a statute closely related to its

pension sur le fondement d'une telle interprétation, n'appartiennent pas aux issues raisonnables possibles du processus décisionnel en cause.

D. Le Tribunal a-t-il commis une erreur dans l'application de la loi aux éléments de preuve?

[112] Puisque j'ai conclu que le Tribunal avait commis une erreur dans le choix du critère de la cause principale pour établir s'il y avait un lien de causalité suffisant entre l'affection alléguée de M^me^ Cole et son service militaire, il est clair que la décision du Tribunal de refuser sa demande de pension d'invalidité ne peut être confirmée.

DÉCISION

[113] Par les motifs qui précèdent, j'accueillerais l'appel, j'infirmerais le jugement du juge de la Cour fédérale daté du 31 mars 2014, et je renverrais l'affaire au Tribunal pour que celui-ci rende une nouvelle décision en conformité avec les présents motifs, avec dépens devant notre Cour et devant la Cour fédérale.

LE JUGE WEBB, J.C.A. : Je suis d'accord.

***

Ce qui suit est la version française des motifs du jugement rendus par

[114] LA JUGE GAUTHIER, J.C.A. (motifs concourants) : Comme mon collègue le juge Ryer, je suis d'avis que le présent appel doit être accueilli et que l'affaire devrait être renvoyée au Tribunal pour que celui-ci rende une nouvelle décision. Toutefois, je souhaite faire de brèves observations sur certaines questions.

[115] Pour ce qui concerne la norme de contrôle, en toute déférence, je ne puis retenir l'idée que la norme de la décision correcte soit la norme applicable à l'interprétation que le Tribunal a faite de l'alinéa 21(2)*a*) de la *Loi sur les pensions*. Comme mon collègue le reconnaît, la Cour suprême enseigne que la norme de la raisonnabilité est présumée jouer lorsqu'un tribunal interprète sa loi

function. While *Dunsmuir v. New Brunswick*, 2008 SCC 9, [2008] 1 S.C.R. 190, states that reviewing courts may rely on the standard of review articulated in prior jurisprudence which has determined that standard on the proper principles, the Court in *Frye v. Canada (Attorney General)*, 2005 FCA 264, 338 N.R. 382, which applied correctness, did not have the benefit of the Supreme Court's subsequent teaching regarding the strength of the reasonableness presumption. I would add that since *Agraira v. Canada (Public Safety and Emergency Preparedness)*, 2013 SCC 36, [2013] 2 S.C.R. 559, at paragraph 48, we no longer apply old authorities on the standard of review but must instead follow the principles worked out in *Dunsmuir* and later jurisprudence. In view of that more recent jurisprudence, I am not persuaded that the presumption of reasonableness has been rebutted in this case.

[116] However, I agree with my colleague that when one properly applies the purposive and contextual method of statutory interpretation, the range of acceptable outcomes is narrow in the present case.

[117] The interpretation of paragraph 21(2)(*a*) of the *Pension Act* required in this appeal is an extricable question of law. As explained by Ryer J.A., however, it is a narrow question in that it is not about the nature or type of relationship that is required between the injury and the disease and a claimant's military service. Rather, it is to determine when the relationship is sufficient to trigger the application of this provision when multiple factors are involved in the onset or aggravation of an injury or disease.

[118] There is no need to examine if and how the expressions "arose out of", "directly connected with" or "attributable to" in paragraph 21(1)(*a*) differ unless these expressions inform the question before us. In my view, they do not.

constitutive ou une loi étroitement reliée à sa mission. Bien que la Cour suprême enseigne, par la jurisprudence *Dunsmuir c. Nouveau-Brunswick*, 2008 CSC 9, [2008] 1 R.C.S. 190, que les cours réformatrices peuvent appliquer la norme de contrôle que la jurisprudence a déjà arrêtée en appliquant les principes appropriés, notre Cour, dans l'arrêt *Frye c. Canada (Procureur général)*, 2005 CAF 264, où elle a appliqué la norme de la décision correcte, n'avait pas le bénéfice de l'enseignement subséquent de la Cour suprême concernant la force de la présomption d'assujettissement à la norme de la raisonnabilité. J'ajouterais que, depuis l'arrêt *Agraira c. Canada (Sécurité publique et Protection civile)*, 2013 CSC 36, [2013] 2 R.C.S. 559, au paragraphe 48, nous n'appliquons plus l'ancienne jurisprudence portant sur la norme de contrôle, mais devons plutôt suivre les principes consacrés par l'arrêt *Dunsmuir* et par la jurisprudence subséquente. Compte tenu de cette jurisprudence plus récente, je ne suis pas convaincue que la présomption d'assujettissement à la norme de la décision raisonnable a été réfutée en l'espèce.

[116] Toutefois, je partage l'avis de mon collègue quant au fait que, lorsque l'on applique correctement la méthode téléologique et contextuelle d'interprétation des lois, les solutions acceptables en l'espèce sont peu nombreuses.

[117] L'interprétation de l'alinéa 21(2)*a*) de la *Loi sur les pensions* requise dans le présent appel est une question de droit qui peut être isolée. Comme le juge Ryer l'a expliqué, toutefois, il s'agit d'une question très précise, en ce sens qu'elle ne concerne pas la nature ou le type de rapport qui est requis entre la blessure et la maladie et le service militaire du demandeur. Il s'agit plutôt de rechercher à quel moment le rapport est suffisant pour faire jouer cette disposition lorsque des facteurs multiples ont contribué à causer ou à aggraver une blessure ou une maladie.

[118] Il n'est point besoin d'examiner en quoi sont différents, le cas échéant, les termes « consécutive [à] » et « rattachée directement [à] », ou « attribuable à » à l'alinéa 21(1)*a*), à moins que ces mots éclairent la question qui nous occupe en l'espèce. À mon avis, tel n'est pas le cas.

[119] It is not disputed that the scheme of the Act applies to an injury or disease that can "arise out" of or, as in this case, be "directly connected to" multiple factors that may or may not all be military service-related. But the wording of the provision before us, read in the overall context of the Act, gives us little indication as to the degree to which the factors that are indeed service-related must have been involved in the onset or aggravation of the disease to trigger the payment of any benefit.

[120] Hence, the purpose of the Act set out in section 2 of the *Pension Act* and section 3 of the VRAB Act become particularly important. I agree with Ryer J.A. that considering the number of multiple etiology diseases, particularly psychological and emotional disease where there is no reasonable scientific method of apportioning precisely degrees of causation, it is not possible to read into paragraph 21(2)(*a*) that compensation is only available if the service-related factors are the primary cause of the disease.

[121] The interpretation offered by Ryer J.A. ensures that the scheme of the Act is not rendered meaningless—insignificant service-related factors cannot be sufficient to trigger the compensation scheme. On the other hand, allowing the mechanism provided by paragraph 21(2)(*a*), when the service-related factors are significant to be triggered, gives effect to Parliament's clear intention that this benefits scheme be liberally construed, so as to ensure that this country's obligation towards members of the forces is met.

[122] The appellant raised a number of other issues directed to the application of this interpretation of paragraph 21(2)(*a*) of the *Pension Act* to the particular facts of this appeal. The panel of the Board which will re-determine this matter is best placed to address these issues.

[119] Il n'est pas controversé entre les parties que le régime de la Loi vise la blessure ou la maladie qui peut être « consécutive » ou, comme en l'espèce, « rattachée directement » à des facteurs multiples qui peuvent être reliés ou pas tous reliés au service militaire. Cependant, le libellé de la disposition dont il est ici question, lu dans le contexte global de la Loi, nous donne peu d'indications quant à savoir à quel degré les facteurs qui sont bel et bien reliés au service doivent avoir contribué à causer ou à aggraver la maladie pour qu'il y ait droit à pension.

[120] L'objet de la Loi énoncé à l'article 2 de la *Loi sur les pensions* et à l'article 3 de la Loi sur le TACRA devient donc particulièrement important. Je conviens avec le juge Ryer que, compte tenu du nombre de maladies à causes multiples, en particulier les maladies psychologiques ou émotionnelles pour lesquelles aucune méthode scientifique raisonnable ne permet d'attribuer précisément des degrés de causalité, il n'est pas possible d'interpréter l'alinéa 21(2)*a*) comme disposant qu'une indemnité ne peut être accordée que si les facteurs reliés au service sont la cause principale de la maladie.

[121] L'interprétation proposée par le juge Ryer assure que le régime de la Loi n'est pas vide de sens — les facteurs négligeables reliés au service ne peuvent pas être considérés comme suffisants pour donner droit à une pension au titre du régime. En revanche, permettre au demandeur de se prévaloir du mécanisme prévu à l'alinéa 21(2)*a*) lorsque les facteurs reliés au service sont importants donne effet à l'intention claire du législateur selon laquelle ce régime de prestations s'interprète de façon libérale, de manière à assurer que l'obligation de ce pays envers les membres des forces est remplie.

[122] L'appelante a soulevé plusieurs autres questions relatives à l'application de cette interprétation de l'alinéa 21(2)*a*) de la *Loi sur les pensions* aux faits de la présente espèce. La formation du Tribunal qui rendra une nouvelle décision dans la présente affaire est la mieux placée pour instruire ces questions.

Representative:	Lisa Laird, BPA
Decision number:	100003937933
Decision type:	Entitlement Review
Location of Hearing:	Halifax, Nova Scotia
Hearing Date:	4 December 2020

The Entitlement Review Panel decides:

HEARING LOSS
TINNITUS

Entitlements granted in the amount of five-fifths for service in the Canadian Armed Forces, Reserve Force.
Section 45, *Veterans Well-being Act*

Compensation is payable effective 1 April 2019, under Section 177 of the Act.

Panel Members: Rose Marie Braden
C. E. Robinson

_____

Rose Marie Braden

INTRODUCTION

The Veteran is 65 years of age and served in the Reserve Force from 14 September 1972 to 1 January 1974.

This claim is brought forward as the Veteran is dissatisfied with the Veterans Affairs Canada (VAC) Official Decision dated 11 June 2019, which denied entitlement for hearing loss and tinnitus, pursuant to Section 45 of the *Veterans Well-being Act*.

PRELIMINARY MATTERS

The hearing was held by teleconference. Due to his profound hearing loss, the Veteran was not able to participate in the hearing.

ISSUES

The issue to be determined is whether the Veteran has provided sufficient evidence on which to establish that his claimed hearing loss and tinnitus conditions arose out of or are directly connected with his military service?

EVIDENCE AND ARGUMENT

In his Application for Disability Benefits, Statement of Case (SOC) 6-7, dated 14 August 2018, the Veteran stated the following in relation to his hearing loss:

> I was in RCEME & exposed to loud noises on the rifle range, midnight manoeuvres; from mine fields; land mines & plastic explosives. The military did not provide me with any hearing protection & because of this, I suffer hearing loss. [*As transcribed*]

With regards to his tinnitus he stated:

> Tinnitus is an accompaniment of my hearing loss, due to my being exposed to loud noises while in the militia & not being provided any hearing protection.

Testimonial Statement

The Veteran provided a statement which detailed the following key facts:

- During military service, he was on the rifle range monthly. Midnight maneuvers were similar to war games. He was exposed to smoke bombs going off.
- He set up explosives including land mines and exploded them. He worked with explosives and land mines on a weekly basis, usually for a period of two days per week.
- He also used a jack hammer to drill holes in stone to place the explosives.
- He was never provided hearing protection during his Reserve Force service.
- He suffered temporary hearing loss subsequent to noise exposure during military service. This lasted 20 to 30 minutes. His ears were also plugged at times for a short period of time.
- He did not report these symptoms because they subsided after a short period of time.
- He does not recall exactly when his tinnitus started or how often he had it but he does recall that it was gradual.
- He has ringing in his ears 5 or 6 times per day now.

- He has had ear infections in both ears due to ear mold in his hearing aids.
- He does not recall why his Medical Statement on Release was not completed.
- Subsequent to military service, he worked as a labourer and in a warehouse as a shipper and receiver for the Department of National Defence from 1977 to 1995. From 1995 to 2018, he worked doing landscaping and doing golf course maintenance and doing dry walling and taping. On the golf course, he was exposed to the noise of a lawn tractor. He wore foam ear plugs every day.
- He didn't have any noise intensive hobbies or recreational activities.
- He had a cochlear implant in his right ear in 2006 because his hearing was getting worse and it was his only option to try to save his hearing.
- He has three siblings. His two brothers have hearing difficulties. They were both in the Reserves also and their hearing loss and tinnitus conditions are directly connected to their military service. No one else in his family has hearing difficulties.
- He does not take any medication that could affect his hearing.
- He concluded that he believes his time in the Reserves contributed to his hearing loss and tinnitus.

Relevant Medical Records

- The Veteran's Report of Physical Examination For Enrolment dated 14 September 1972, SOC 20-21, indicated no hearing issues. He was rated H1.
- There is no release audiogram available.
- An Innovative Hearing Solutions Inc. audiogram dated 10 September 2018, SOC 11, prepared by audiologist, Briana Lasseter, indicated profound bilateral hearing loss.
- His Medical Questionnaire: Tinnitus prepared by audiologist, Briana Lasseter, dated 10 September 2018, SOC 12, indicated tinnitus being present for over 40 years. It is intermittent tinnitus, present daily but not all day long, affecting one or both ears.

New Evidence

The Advocate provided additional documentation on the Veteran's behalf, specifically:

- Testimonial Statement, ER-A1;
- Medical opinion prepared by audiologist, Briana Lasseter, Innovative Hearing Solutions Inc. dated 15 June 2020, ER-A2;
- Consent and Waiver, ER-A3;
- Letter from the Veteran dated 5 December 2019 with 2005 audiogram, ER-A4;
- VAC Hearing Loss and Tinnitus policy, ER-Attach-A1;
- VAC Entitlement Eligibility Guidelines (EEGs) on Hearing Loss, ER-Attach-A2
- VAC EEGs on Tinnitus, ER-Attach-A3.

Submissions by the Advocate

The Advocate was seeking full entitlement for both conditions due to noise exposure during military service, consistent with the current Hearing Loss and Tinnitus policy.

The Advocate submitted that the Veteran had no hearing issues on enrolment. No audiograms were performed during service or on release. The first audiogram available post service was in 2005 which showed profound hearing loss. His Medical Questionnaire: Tinnitus dated September 2018 indicated tinnitus present for more than 40 years.

The Veteran served in the Reserves from 1972-1974, and provided a statement in ER-A1 detailing evidence in respect to his hearing loss. Regarding family history, his two brothers are the ones with hearing loss and both were in military service and have been granted entitlement. His medications that he takes for his heart do not impact his hearing. He had a cochlear impact. His ear infections were due to his hearing aids.

The Advocate read the Veteran's statement, ER-A4. She also referred to the Veteran's audiogram dated 6 May 2005, which showed profound hearing loss.

The Veteran was exposed to loud noises of explosives, artillery and a jack hammer while serving with no hearing protection.

In regards to ER-A2, the letter from the audiologist, his current hearing loss is multi-factorial; his military noise exposure would be a factor. The Advocate submitted that this is consistent with the Merck Manual Professional Version*,* SOC 26*.*

The Advocate further submitted that as indicated in the EEGs, cause can't be determined from an audiogram alone. Higher frequency noises cause more damage than lower. Noise levels above 140 cause damage immediately and he was exposed to the sound of a jack hammer which is above 130. Therefore, a single exposure could have caused damage.

The Advocate submitted that paragraph 4 of the current Hearing Loss and Tinnitus policy applies:

> 4. Where it is determined that hearing loss was documented during service or at the time of discharge and/or service is reasonably found to be the initiating factor causing the current hearing loss disability, then full entitlement to disability benefits may be awarded.

In respect to his claim for tinnitus, the Veteran did not complain but did experience loss of hearing and feeling plugged for short periods. He has been struggling with tinnitus for 40 years. He can't recall exactly when it started.

ANALYSIS/REASONS

The Panel has reviewed all of the evidence and has also taken into consideration the Advocate's submissions. In doing so, the Panel has applied the requirements of section 39 of the *Veterans Review and Appeal Board Act.* This section requires the Panel to:

> (*a*) draw from all the circumstances of the case and all the evidence presented to it every reasonable inference in favour of the applicant or appellant;
> (*b*) accept any uncontradicted evidence presented to it by the applicant or appellant that it considers to be credible in the circumstances; and
> (*c*) resolve in favour of the applicant or appellant any doubt, in the weighing of evidence, as to whether the applicant or appellant has established a case.

This means that in weighing the evidence before it, the Panel will look at it in the best light possible and resolve doubt so that it benefits the Applicant. The Federal Court has confirmed, though, that this law does not relieve applicants of the burden of proving the facts needed in their cases to link the claimed condition to service. The Panel does not have to accept all evidence presented by an applicant if it finds that it is not credible, even if it is not contradicted.[1]

In determining whether entitlement will be granted, the Panel must answer the following three questions:

1. Are there valid, existing diagnoses of the claimed conditions?
2. Do the claimed conditions constitute permanent disabilities? and,
3. Were the claimed conditions caused, aggravated or contributed to by military service?

If the answer to any of these three questions is no, then the Panel must conclude that the Veteran has not met the burden of showing that entitlement should be granted.

The VAC Entitlement Eligibility Guidelines for Hearing Loss (modified January 2019) read in part:

> For VAC purposes, normal hearing exists where there is decibel loss of 25 dB or less at all frequencies between 250 and 8000 hertz.
>
> For VAC purposes, a hearing loss disability exists when there is a Decibel Sum Hearing Loss (DSHL) of 100 dB or greater at frequencies of 500, 1000, 2000 and 3000 Hz in either ear, or 50 dB or more in both ears at 4000 Hz.
>
> For VAC purposes, hearing loss exists when there is a decibel loss greater than 25 dB at frequencies between 250 and 8000 hertz (inclusively), and this loss is not sufficient to meet VAC's definition of a hearing loss disability.

The VAC Hearing Loss and Tinnitus policy, effective 1 April 2019 indicates, in part:

General

2. In order to consider whether hearing loss is related to service, the Veteran/member must have a current hearing loss disability.
3. In the case of Veterans/members having presented with permanent service-related hearing loss in service on discharge, the Veterans/members must demonstrate that they now suffer from a hearing loss disability.
4. Where it is determined that hearing loss was documented during service or at the time of discharge and/or service is reasonably found to be the initiating factor causing the current hearing loss disability, then full entitlement to disability benefits may be awarded.
5. In the case of normal hearing during service, any hearing loss that occurs after service is considered post-discharge in origin and is not considered related to service.
6. If there is evidence of a hearing loss disability prior to service (pre-enlistment) partial entitlement, may be considered for any further service-related aggravation. There would be no need to consider other possible contributing factors.
7. Although noise is the most common factor, it is not the only possible service-related factor which could cause a permanent service-related hearing loss or service-related hearing loss disability. A number of factors can contribute to hearing loss; for example physical injury, diseases including infections, obstructions in the ear canal and middle ear, taking certain medications and exposure to certain chemicals. (For more information regarding hearing loss factors/considerations, please see Entitlement Eligibility Guidelines (EEGs) for Hearing Loss.
8. The maximum award a Veteran/member can receive is full entitlement.

Hearing Loss Analysis

The Veteran's diagnosis of hearing loss is not in dispute and the Panel is satisfied, given the ongoing nature of the condition that it constitutes a disability. The final question to answer is whether a service relationship can be established.

In the context of a claim for hearing loss attributable to noise exposure, the above Guidelines and policy, requires the Veteran to establish that he had a service-related

hearing loss (decibel loss greater than 25) in service or on discharge in the frequencies between 2000 and 6000 hertz (Hz), or service is reasonably found to be the initiating factor causing the current hearing loss disability. If established and the Veteran has a current hearing loss disability, full entitlement is warranted.

The Veteran enrolled with no hearing issues. He provided a statement describing his noise exposure during service which included rifles, jack hammers and explosives. Also, he stated that during service, no hearing protection was provided. He had temporary hearing loss and muffled hearing subsequent to noise exposure.

The report of audiologist, Briana Lasseter dated 15 June 2020, ER-A2, concluded that "while a definitive cause of (the Veteran's) hearing loss and tinnitus cannot be determined, his service-related noise exposure could have played a role and can not be ruled out based solely on his audiogram". *(information added)*

The Merck Manual Professional Version provides the following explanation regarding how noise can impact hearing loss, SOC 31:

> **Noise** can cause sudden or gradual sensorineural hearing loss. In acoustic trauma, hearing loss results from exposure to a single, extreme noise (eg, a nearby gunshot or explosion); some patients develop tinnitus as well. The loss is usually temporary (unless there is also blast damage, which may destroy the tympanic membrane, ossicles, or both). In noise-induced hearing loss, the loss develops over time because of chronic exposure to noise > 85 decibels (dB—see Sound Levels). Even before hearing loss can be documented, noise exposure can damage auditory neurons and their synapses on hair cells; this damage is referred to as "hidden hearing loss" or "synaptopathy," and patients may notice difficulty hearing in noisy environments and have accelerated age-related hearing loss.

Given the evidence above, the Veteran's military service can reasonably be found to be the initiating factor causing the current hearing loss disability. Accordingly, full entitlement, or entitlement on a five-fifths basis, is merited.

Tinnitus Analysis

The Veteran's diagnosis of tinnitus is not in dispute and the Panel is satisfied, given the ongoing nature of the condition that it constitutes a disability. The final question to answer is whether a service relationship can be established.

In determining entitlement, the Panel is guided by the Veterans Affairs Canada (VAC) EEGs for Tinnitus. These Guidelines indicate the following causes/aggravation of tinnitus as follows:

A. Causes And / Or Aggravation

….

1. Exposure to at least one episode of acoustic trauma sufficient to have caused some decibel loss of hearing (permanent or temporary) just prior to clinical onset or aggravation

   Acoustic trauma means a condition of sudden aural damage resulting from short-term intense exposure, or a single exposure, to loud noise such as that made, at close quarters, by:

   - fireworks
   - small arms fire
   - gunfire
   - artillery fire
   - exploding grenades, mines or bombs
   - blast injury

2. Exposure to noise, other than acoustic trauma, that is of sufficient intensity and duration to cause hearing loss of 25 decibels or more at 3000, 4000 or 6000 frequency [in the ear(s) with tinnitus], prior to clinical onset or aggravation.

The Veteran enrolled with normal hearing and was rated H1. Although the Veteran does not recall exactly when his tinnitus started, he does know that it was more than 40 years ago, which would be at least the late 1970s. Despite missing the exact timing of the onset, the Panel finds that the Veteran's statement in respect to his noise exposure during service is consistent with criteria one of the EEGs, exposure to at least one episode of acoustic trauma sufficient to have caused some decibel loss of hearing just prior to clinical onset. The Panel notes that criteria one does not require a particular degree of decibel loss, and does not require decibel losses to be permanent in nature. As military medical examinations occur annually or less, it is entirely plausible that a temporary threshold shift occurred, yet was never detected. Every reasonable inference is drawn in favour of the Veteran. Given the evidence in respect to criteria one, the Panel concludes that there is sufficient evidence to relate the Veteran's tinnitus to his military service.

In consideration of the above mentioned factors, and in drawing all inferences from the evidence favourable to the Veteran, and in the weighing of the evidence resolving all doubt in favour of the Veteran, the Panel rules to grant pain and suffering compensation on a five-fifths basis for the claimed condition of tinnitus, Reserve Force service.

DECISION

The Review Panel grants pain and suffering compensation in the amount of five-fifths for Hearing Loss and Tinnitus under Section 45 of the *Veterans Well-being Act*.

EFFECTIVE DATE – RETROACTIVITY

The compensation granted by this Panel is payable under paragraph 51(1)(a) of the *Veterans Well-being Act* on 1 April 2019. Sections 174 and 177 of the Act provide that this application for compensation was deemed to be made on 1 April 2019.

There is no entitlement to an additional award under subsection 51(2) of the Act, because there was no delay in excess of three years between this Panel's decision and the date of application.

Applicable Statutes:

Veterans Well-being Act, [S.C. 2005, c.21.]

Section 45
Section 51

Veterans Review and Appeal Board Act, [S.C. 1987, c. 25, s. 1; R.S.C. 1985, c. 20 (3rd Supp.), s. 1; S.C. 1994-95, c. 18, s. 1; SI/95-108.]

Section 3
Section 25
Section 39

Exhibits:

ER-A1: Testimonial statement (7 pages)

ER-A2: Medical opinion prepared by audiologist, Briana Lasseter, Innovative Hearing Solutions Inc. dated 15 June 2020 (2 pages)

ER-A3: Consent and Waiver for Teleconference Hearing or in Absentia Hearing (1 page)

ER-A4: Letter from the Veteran dated 5 December 2019 with attached audiogram (3 pages)

Attachments:

ER-Attach-A1: VAC Hearing Loss and Tinnitus policy (7 pages)

ER-Attach-A2: VAC EEGs on Hearing Loss (19 pages)

ER-Attach-A3: VAC EEGs on Tinnitus (11 pages)

[1] *MacDonald v. Canada (Attorney General)* 1999, 164 F.T.R. 42 at paragraphs 22 & 29; *Canada (Attorney General) v. Wannamaker* 2007 FCA 126 at paragraphs 5 & 6; *Rioux v. Canada (Attorney General)* 2008 FC 991 at paragraph 32.

Veterans Review and Appeal Board

Representative:	Suzanne Newman, BPA
Decision number:	100004407577
Decision type:	Entitlement Review
Location of Hearing:	Charlottetown, Prince Edward Island
Hearing Date:	25 October 2023

The Entitlement Review Panel decides:

TINNITUS

Entitlement granted in the amount of five-fifths for service in the Canadian Armed Forces, Regular Force, with effect from 1 October 2020.
Section 45, *Veterans Well-being Act*

Compensation is payable under subsection 51(1) of the Act, on the later of the first day of the month on which the application for compensation was made, or on the first day of the month that is three years before the date of this decision.

Panel Members: R. D. Boughen
C. E. Robinson

_____

R. D. Boughen

INTRODUCTION

This claim is brought forward as the Veteran is dissatisfied with the Veterans Affairs Canada (VAC) decision dated 13 May 2020 which denied entitlement for tinnitus.

PRELIMINARY MATTERS

This matter has proceeded under the Veterans Review and Appeal Board Simplified Model[1] by written submission[2].

ISSUE

Is entitlement warranted for the Veteran's condition?

EVIDENCE AND ARGUMENT

The Veteran served in the Reserve Force from 11 November 1986 until 4 April 1987 and the Regular Force from 3 March 1989 to 10 October 2009. During his service he was deployed to three Special Duty Areas (SDAs):

- Special Duty Area (Syria) – 10 March 2000 to 4 September 2000
- Special Duty Area (Bosnia) – 23 September 2003 to 29 March 2004
- Special Duty Area (Afghanistan and surrounding area) – 12 February 2005 to 28 July 2005

The Veteran originally applied for entitlement on 12 November 2019. At that time he indicated his tinnitus was as a result of exposure to noise when on exercises and operations. He was exposed to such things as artillery simulators, thunder flashes and small arms fire.

On 13 May 2020, the Veteran was denied entitlement by VAC because they found insufficient evidence of exposure to enough noise during service to cause permanent decibel losses.

The Veteran served for 20 years and the Panel notes that there are relatively few audiograms throughout his career.

The Veteran's tinnitus diagnosis is contained in a November 2019 Medical Questionnaire.

In October 2022, Karen Enman, Doctor of Audiology (ER-Ex-G2), opined that the Veteran's hearing loss and tinnitus are related to his military noise exposure.

The Advocate suggests full entitlement is warranted.

ANALYSIS/REASONS

In determining whether entitlement will be granted, the Panel must ask three questions for which there must be an affirmative answer to all three:

1. Is there a valid, existing diagnosis of the claimed condition?
2. Does the claimed condition constitute a permanent disability?
3. Was the claimed condition caused, aggravated or contributed to by Regular Force service?

The Panel finds there is a valid diagnosis and that the condition is permanent and disabling.

Veterans Review and Appeal Board (VRAB) Panels consider the criteria within the VAC Entitlement Eligibility Guidelines (EEGs), unless there is a compelling reason submitted not to. The EEGs are based on consensus from credible medical research and literature, as well as guidelines from other disability compensation bodies in Canada, the United States and Australia. Applying them achieves a significant measure of consistency in disability compensation decisions. No compelling reason has been submitted by the Veteran or his Advocate for setting aside the respective EEGs; therefore, the Panel will consider them.

One of the eligibility criteria for tinnitus clearly states that entitlement may be established when there is evidence of "acoustic trauma sufficient to have caused some decibel loss of hearing (**permanent or temporary**) just prior to clinical onset or aggravation" [*Emphasis added*]. The sources of noise can include, but are not limited to, small arms fire, gunfire, artillery fire, exploding grenades, mines or bombs, or blast injury. This specific criterion does not require a particular degree of decibel loss and does not require decibel losses to be permanent in nature. By the very nature of the frequency of the Veteran's periodic health assessments and audiograms, occurring annually or less, it is entirely plausible that a temporary threshold shift can occur, yet never be detected during those medical examinations.

By virtue of his occupation and his general military requirements, it is accepted that the Veteran would have had occasion to be exposed to loud sources of noise. In the Veteran's case, he was exposed to loud noises such live fire exercises, operating heavy vehicles as well as small arms and heavy weapons fire.

The Panel acknowledges that the Veteran was exposed to loud noises during service with the Canadian Armed Forces.

The Panel finds that it is reasonable to infer that the Veteran's tinnitus arose out of military service.

In drawing all inferences from the evidence favourable to the Veteran and in weighing the evidence while resolving all doubt in favour of the Veteran,[3] the Panel rules to grant full entitlement for the claimed condition.

DECISION

The Panel grants an award in the amount of five-fifths for the Veteran's tinnitus under Section 45 of the *Veterans Well-being Act* for Regular Force service.

EFFECTIVE DATE

The Panel awards retroactivity effective 1 October 2020.[4]

Applicable Statutes:

Veterans Well-being Act, [S.C. 2005, c.21.]

Section 45
Section 51

Veterans Review and Appeal Board Act, [S.C. 1987, c. 25, s. 1; R.S.C. 1985, c. 20 (3rd Supp.), s. 1; S.C. 1994-95, c. 18, s. 1; SI/95-108.]

Section 3
Section 25
Section 39

Exhibits:

ER-Ex-G1:	Audiogram dated 7 October 2022 (one page)
ER-Ex-G2:	Letter from Karen Enman, Doctor of Audiology, dated 20 October 2022 (four pages)

APPEAL RIGHTS

If you are dissatisfied with this decision, you may appeal it to an Appeal Panel of the Veterans Review and Appeal Board, which may affirm, vary or reverse the decision.

In pursuing this right of appeal, you may be represented, free of charge, by the Bureau of Pensions Advocates or a service bureau of a veterans' organization or at your expense by any other representative.

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[1] In 2018, Veterans Affairs Canada implemented updated policies and Entitlement Eligibility Guidelines in respect of fractional entitlement and Hearing Loss, which resulted in a larger volume of cases where the primary argument being advanced was consideration of the more generous adjudicative environment. These cases involved narrow issues, straightforward arguments, and predictable outcomes. The Veterans Review and Appeal Board implemented a Simplified Model, which involves a simplified hearing process and a simplified decision. The Simplified Model allows the Board to group these less complex cases, where the outcome is predictable, allowing for a larger volume of cases to be heard in a shorter period of time. This streamlined process allows cases to be heard more quickly and will result in Veterans, CAF and RCMP Members and their families receiving decisions sooner, and increase the Board's capacity and time to address more complex cases.
[2] Pursuant to Section 20 of the *Veterans Review and Appeal Board Act*.
[3] Pursuant to Section 39 of the *Veterans Review and Appeal Board Act*.
[4] Pursuant to subsection 51(1) of the *Veterans Well-being Act* which allows for retroactivity from the later of the first day of the month in which the application is made or the day that is three years before the first day of the month in which compensation is granted.