

## The functional age of hearing loss in a mouse model of presbycusis. II. Neuroanatomical correlates

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### Abstract

This report relates patterns of age-related outer hair cell (OHC) loss to auditory behavioral deficits in C57BL/6J mice. Hair cell counts were made from serial sections of the cochlear partition in three subject groups representing young (2–3 months), middle (8–9 months), and old ages (12–13 months). The cochlear location of OHC counts was determined from three-dimensional computerized reconstructions of the serial sections. Comparisons of the topographic distribution of surviving OHCs across the subject groups confirmed an orderly base-to-apex progression of cochlear degeneration that is well known in this mouse strain. All mice appeared to follow the same progression of OHC loss, although subjects showed considerable variation in the rate at which they advanced through a uniform sequence of structural changes. Behavioral implications of the magnitude and location of OHC loss were investigated by correlating the histological status of individual mice with sound detection thresholds from the same subjects [Hear. Res. 183 (2003) 44–46]. The analysis revealed regionalized patterns of OHC loss that were correlated with frequency-dependent changes in hearing thresholds, and validates the use of ‘functional age’ as an indicator of age-related cochlear degeneration and dysfunction. In the absence of physiologically defined cochlear frequency maps for C57BL/6J mice, these structure–function correlation techniques offer an alternative approach for linking anatomical results to hearing abilities.

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*Key words:* Outer hair cell; Age-related hearing loss; Presbycusis; Cochlear frequency map

### 1. Introduction

The patterns of hearing loss and cochlear degeneration in C57BL/6J mice mimic human presbycusis. A rapid progression of hearing loss begins at high frequencies by age 2–3 months, and severely affects low frequencies by age 12–13 months (Henry and Chole, 1980; Hequembourg and Liberman, 2001; Li and Borg, 1991). During this time period, a topographically organized loss of outer hair cells (OHCs) advances from

the base to the apex of the cochlea (Henry and Chole, 1980; Spongr et al., 1997). Although these observations suggest a systematic relationship between structural changes in the organ of Corti and functional hearing deficits, previous attempts to correlate age-related hearing loss with specific patterns of cochlear degeneration have met with mixed success. A major obstacle for correlation methods has been the significant inter-subject variability that is noted for the rate of hearing loss in mice and other animal models of presbycusis. This, too, is a feature of age-related hearing loss in humans.

The present histological study revisited this clinically relevant dilemma with the most elementary index of inner ear pathology. Survival rates of OHCs were measured along the cochlear partition in age-matched groups of C57BL/6J mice to quantify the magnitude and location of the degenerative effects that give rise

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Abbreviations: IHC, inner hair cell; KFeCN, potassium ferri-cyanide; OHC, outer hair cell; OsO<sub>4</sub>, osmium tetroxide

to functional deficits. This traditional anatomical approach confirmed previously described patterns of OHC loss.

A new perspective on the functional implications of structural changes in the aging cochlea was gained by interpreting histological results in the context of psychophysical assessments of hearing thresholds in C57BL/6J mice. A long-term behavioral study followed the progression of hearing loss through an orderly sequence that began with the development of performance deficits in background noise, and then advanced to increasingly higher tone detection thresholds in quiet. The behavioral testing of individual subjects was stopped at different stages in this progression to allow histological evaluation of the current status of cochlear degeneration. A description of these behavioral measures can be found in the companion paper by Prosen et al. (2003).

Age-related shifts in the pure-tone detection thresholds of behaviorally characterized mice were correlated with OHC survival rates. When this analysis was applied to regionalized OHC loss at intervals along the cochlear partition, systematic variations in the strength of the correlations revealed a topographic organization that corresponded well to the presumed transduction sites of behavioral threshold frequencies. Because physiologically defined cochlear frequency maps are not presently available in mice, these results offer an alternative method for directing more sophisticated anatomical measures to functionally defined sites of impending hearing loss. For example, age-related cell death in the inner ear may be associated with apoptosis and thus predicted by specific markers of DNA degradation (Usami et al., 1997). Similarly, hearing loss in the C57BL/6 strain is correlated with localized changes in cochlear energy metabolism that can be revealed with dehydrogenase histochemistry (McFadden et al., 2001). Correlations based on this functional anatomy may prove especially useful in isolating cellular events in the progression of hearing loss that precede OHC degeneration.

## 2. Materials and methods

### 2.1. Subjects

The topography of OHC loss was assessed along the length of the organ of Corti in 19 C57BL/6J mice. Fifteen subjects received 6–12 months of prior psychoacoustic testing before being evaluated with histological procedures at ages ranging from 8 to 13 months (Prosen et al., 2003). The remaining subjects consisted of three young mice with normal ABR thresholds (ages 2–3 months) and one old mouse with elevated ABR thresh-

olds (age 13 months). All procedures for the harvesting and histological preparation of cochlear tissue were conducted in accordance with NIH guidelines and were approved by the Institutional Animal Care and Use Committee of Johns Hopkins University.

### 2.2. Histological preparation

Cochlear perfusions were completed under surgical anesthesia (125 mg/kg ketamine and 12.5 mg/kg xylazine in 14.25% ethanol, i.p.). An incision was made over the left pinna to expose the ear canal and the middle ear was entered at the lateral rim of the bony canal. The ossicles were removed to gain access to the cochlear promontory. A route for the circulation of perfusates (1% OsO<sub>4</sub>/1% KFeCN) was created by perforating the oval window and fenestrating the cochlear apex. Fixative was gently infused into the scalae. After a similar *in vivo* perfusion of the right ear, the temporal bones were removed and submersed in fixative for several hours. Subjects showed no signs of outer or middle ear pathology during temporal bone dissections.

Histological evaluations were performed on serial sections of the organ of Corti in 16 mice. The cochleae

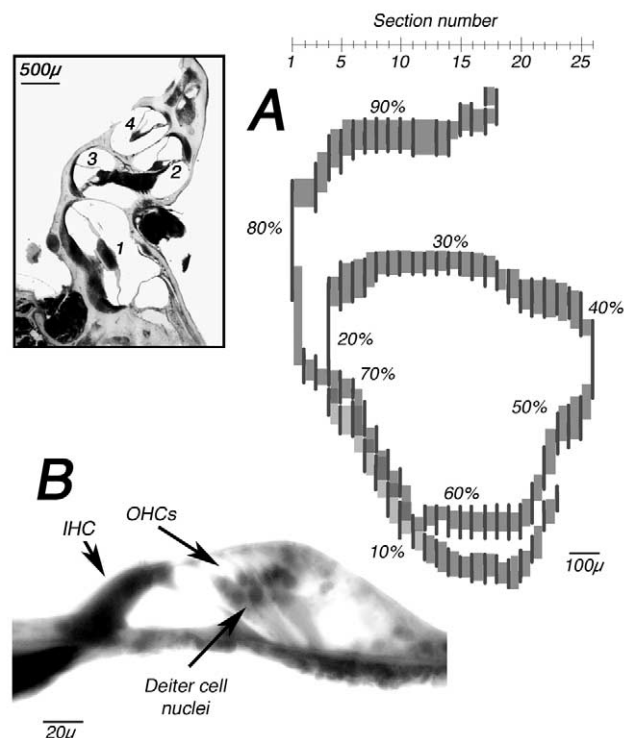


Fig. 1. Methods for evaluating the magnitude and location of OHC loss. (A) Computer reconstruction of the cochlear spiral. A three-dimensional image was created by combining serial sections (inset). (B) Photomicrograph showing intact organ of Corti at an apical location. The OHCs show a 1:1 relationship with Deiter cells. IHC, inner hair cell; OHCs, outer hair cells.

were extracted from the temporal bones and placed in 0.1 M EDTA. Once decalcified, the cochleae were embedded in plastic to permit the present light microscopic analysis and future evaluation with transmission electron microscopy. These methods have been described in detail by Hequembourg and Liberman (2001). The process involved dehydration with graded concentrations of ethanol, infiltration with a 1:1 ratio of propylene oxide and Araldite, and final embedding in full-strength Araldite. The cochleae were cured at 60°C for 24 h, cut in 40- $\mu$ m paramodiolar sections, and mounted in series between sheets of ACLAR<sup>®</sup> fluoropolymer film to permit examination with both light and electron microscopy (see inset in Fig. 1). No staining beyond the osmium perfusate was performed.

The cochleae were reconstructed from serial sections using a computerized imaging system (NIH Image and Vaytech Inc. Voxblast). The cochlear duct and associated landmarks in each serial section were traced under a drawing tube and digitally photographed. The resulting two-dimensional views were combined into a three-dimensional image that could be spatially rotated to facilitate distance measurements of the cochlear coil from base to apex (Fig. 1A). The location of OHCs in individual sections was normalized in terms of percent apical distance relative to total cochlear length.

The OHCs were counted under a light microscope by adjusting the plane of focus through the 40- $\mu$ m-thick section of the organ of Corti (Fig. 1B). To avoid multiple counts of the same cell, the number of surviving cells was limited to OHCs and supporting cells with visible nuclei. Because OHCs and Deiter cells show a 1:1 relationship in the intact cochlea, the percentage of missing OHCs was estimated from decreased OHC counts relative to Deiter cells. This calculation is described by Eq. 1:

$$\% \text{OHC loss} = (\text{Deiter cells} - \text{OHCs}) / (\text{Deiter cells}) \times 100(1)$$

Missing OHCs were estimated from an expected 3:1 relationship with outer pillar cell nuclei in sections where clear Dieter cell counts were unavailable. Reported values are based on the average OHC loss in five adjacent sections. These measures were centered on 10% distance intervals along the length of the cochlear duct, and at the presumed transduction sites for 8- and 16-kHz tones based on estimates of the mouse cochlear frequency map (Ehret, 1975; Ou et al., 2000). Hearing sensitivity at the two frequencies was assessed with behavioral procedures that were completed within 3 days of histological preparation (Prosen et al., 2003).

The decalcified cochleae of three mice were dissected under microscopy in 0.1 M phosphate buffer producing pie-shaped pieces of the organ of Corti and spiral ganglion. These surface preparations were dehydrated as previously described and mounted on glass slides in

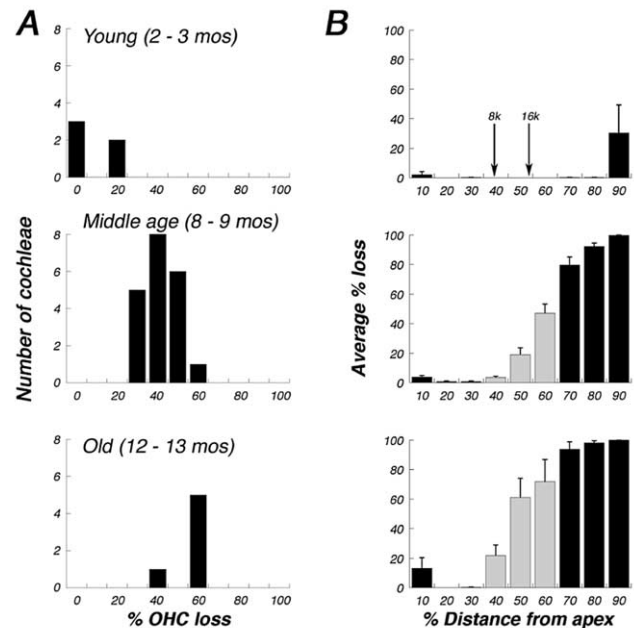


Fig. 2. Effects of age on the magnitude and location of OHC loss. (A) Distribution of total OHC loss within young, middle-age, and old groups. (B) Distribution of average OHC loss along the cochlear partition. Arrows point to estimated transduction sites for 8- and 16-kHz stimuli (Ehret, 1975). Major differences were observed in the OHC survival rates of older subjects at these intermediate cochlear locations (gray-filled histograms).

small drops of Epon. After drying for 2 h at 60°C, the full length of the organ of Corti was traced and measured, and the percentage of missing OHCs was estimated at 10% intervals. Differences in absolute cochlear length measurements between reconstructed cochleae and surface preparations were corrected by calculating distances in terms of percentage of total cochlear length. The consistency of results across the two counting methods confirmed the reliability of three-dimensional reconstructions.

### 3. Results

Light microscopy revealed patterns of presbycusis-like OHC loss that are well known in the C57BL/6J mouse strain. Generalized trends in this age-related hearing loss have been summarized by grouping OHC counts for young (2–3 months), middle-age (8–9 months), and old mice (12–13 months). On average, young mice exhibited less than 20% total OHC loss (Fig. 2A), which was confined to the most basal 10% of the cochlea (Fig. 2B). Middle-age mice displayed varying degrees of OHC loss that ranged from as little as 25% to as much as 60%. These transitional zones with highly variable patterns of hair cell loss are highlighted by a light gray fill in Figs. 2 and 3. In part, the

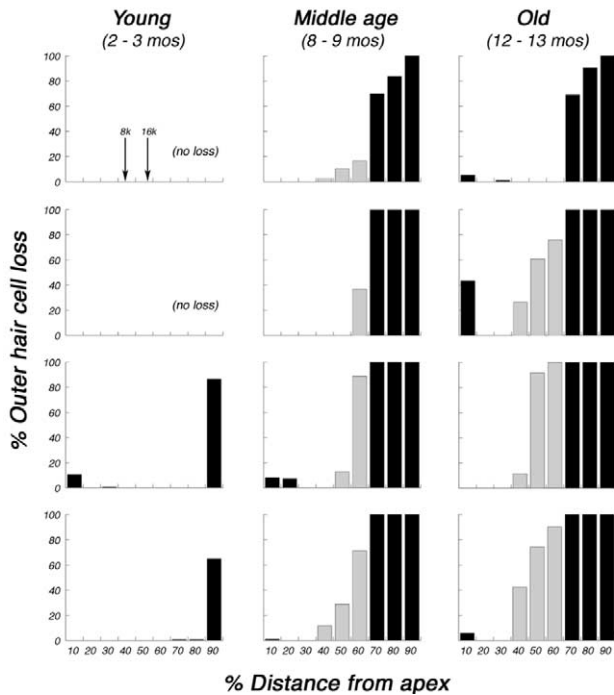


Fig. 3. Individual differences in the magnitude and location of OHC loss. Subjects in the upper rows represent minimum loss within the three age groups. Maximum loss is shown in the lower rows.

increased loss relative to young mice reflected a topographically organized progression that left the basal 30% of the cochlea essentially devoid of OHCs. Old mice showed further OHC loss at intermediate cochlear locations between 30 and 60% distance from the apex.

The generalized trends of the three age groups fail to capture the considerable variability in OHC loss that was observed in age-matched subjects. Examples of these individual differences are presented in Fig. 3. The upper to lower rows of the figure represent minimum to maximum levels of OHC loss within each age group. Mice in the 2–3-month group showed an equal likelihood of no loss or substantial loss at the most basal cochlear locations. One mouse in the 12–13-month group had less OHC loss at intermediate cochlear locations than the four younger subjects in the 8–9-month group. These data point out the inherent variability of histological results that are obtained with age-based sampling techniques.

Advancing OHC loss followed a consistent topographical sequence. This relationship is illustrated in Fig. 4A, which plots total OHC loss as a function of the edge of loss (i.e., the most apical cochlear location with no surviving OHCs). Each data point represents one cochlea. The subject's age is indicated by symbol type. Although the most pervasive hearing loss was observed among older subjects, there was considerable intermingling of data from middle-age and old mice. In all subjects, the magnitude of total OHC loss was

systematically related to the edge of OHC loss and therefore could be accurately predicted by one statistically significant linear regression ( $P < 0.001$ ). These results suggest that a uniform sequence of structural changes was conserved across subjects in spite of highly individualized rates of hearing loss.

The functional significance of this basic pattern of

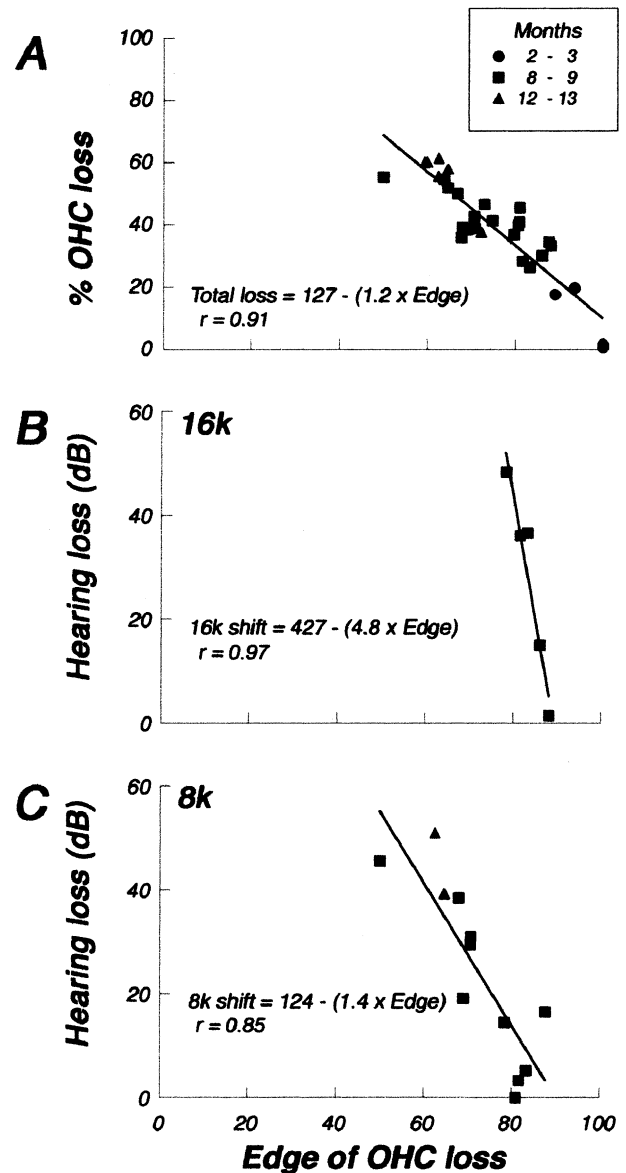


Fig. 4. Correlations in OHC loss and behavioral thresholds. (A) The percentage of missing OHCs as a function of the apical location of complete OHC loss (i.e. the edge of loss). A single linear regression (line and equation) produced a statistically significant fit for data from all three age groups ( $P < 0.05$ , Student's  $t$ -test). (B,C) The magnitude of behavioral threshold shifts at 16 and 8 kHz as a function of the edge of OHC loss. Linear regressions for both data sets were statistically significant ( $P < 0.05$ , Student's  $t$ -test). The reduced sample size at 16 kHz reflects the lack of recent behavioral thresholds from middle- and old-age subjects. No thresholds were available for young mice.

OHC loss was investigated by correlating histological results to behavioral assessments of hearing sensitivity (Fig. 4B,C). This analysis was only possible for mice in the middle and old age groups because behavioral thresholds were tracked for a minimum of 8 months in all subjects. For structure–function correlations of this nature, our measures of OHC loss were based on the cochlea with the most surviving OHCs in each subject, on the assumption that free-field behavioral thresholds were likely to reflect the functionality of the more intact ear. The magnitude of the hearing loss is described in terms of threshold shifts. These measures were calculated by subtracting the subject's most sensitive threshold, usually recorded at a young age, from a final threshold that was obtained just prior to histological preparation.

The structure–function correlation for 16-kHz threshold shifts was limited to five mice in the 8–9-month age group (Fig. 4B). The remaining subjects had lost all hearing at this frequency or were tested at different frequencies immediately prior to histological evaluation. Because hearing sensitivity was maintained at 8 kHz, behavioral data from 12 mice were available for the 8-kHz regression. The correlation coefficients of both linear regressions were statistically significant ( $t$ -statistic,  $P < 0.05$ ).

Correlations between the edge of OHC loss and hearing sensitivity were influenced by the frequency of behavioral testing. Large threshold shifts at 16 kHz were associated with OHC loss in the basal cochlea (i.e. an edge of loss 70–90% from the apex). The same magnitude of hearing loss was only observed at 8 kHz when the edge of the lesion extended to more intermediate cochlear distances of 50–70%. These results led to the possibility that a more detailed regionalized analysis of OHC loss could be used to map the tonotopic organization of functional hearing loss in C57BL/6J mice.

Regionalized effects of cochlear pathology were evaluated by correlating behavioral thresholds with OHC loss at intervals along the cochlea. The correlations in Fig. 5A were based on the five 16-kHz threshold shifts in Fig. 4B and OHC loss restricted to cochlear locations 40, 70, and 90% distance from the apex. Correlations were absent at the 40 and 90% apical locations because the five middle-age mice displayed either too little or too much OHC loss at these locales. By contrast, a statistically significant linear correlation was observed at the 70% location ( $r = 0.96$ ,  $P < 0.05$ ).

The spatial tuning of the regionalized structure–function correlations was revealed by plotting the correlation coefficient ( $r$ ) of the linear regressions as a function of OHC location. These results are shown in Fig. 5B. As previously noted, no significant correlations were observed at distances less than 50% (Fig. 2B). The sharp rise in the statistic at cochlear distances between

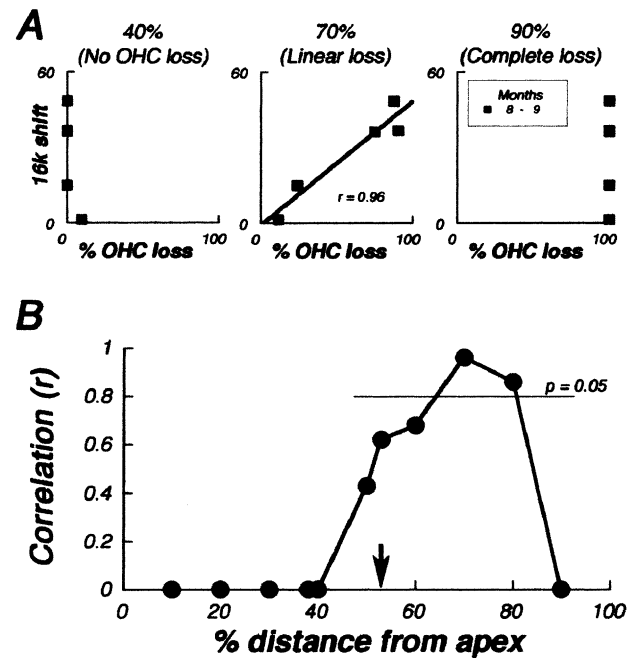


Fig. 5. Effects of regional OHC loss on the detection of 16-kHz tones. (A) Correlation of 16-kHz detection thresholds with OHC loss at 40, 70, and 90% distance from the apex. Each symbol indicates results from one middle-age mouse. The correlation coefficient ( $r$ ) for a linear regression of data at the 70% location was statistically significant. (B) Correlation coefficients for 16-kHz threshold shifts and OHC loss along the entire cochlear partition. Values above the horizontal line were statistically significant ( $P < 0.05$ ,  $n = 5$ ). The arrow points to the expected transduction site for 16-kHz stimuli (Ehret, 1975).

50 and 80% reflects the higher probability of OHC loss at intermediate locations (as shown in the middle column of Fig. 3) and its relationship to a 16-kHz threshold shift. An upper limit of the tonotopic relationship was observed at cochlear distances exceeding 80% where OHC survival rates approach 0% (Fig. 5A). Only regionalized correlations at the 70 and 80% locations attained statistical significance given the small sample size of behaviorally characterized mice with remaining 16-kHz sensitivity ( $n = 5$ ,  $P < 0.05$ ).

Ehret (1975) calculated a 53% apical location for the transduction of 16-kHz stimuli by transposing the audible frequency range of mice to total cochlear length. This predicted location corresponds well to the most apical location of OHC loss in middle-age mice (shown by the arrow in Fig. 2B), and the apical margin of a structure–function correlation with 16-kHz threshold shifts (Fig. 5B). If age-related hearing loss follows an orderly progression from the base to the apex of the cochlea in C57BL/6J mice as it is widely assumed, it is not surprising that the strongest correlations are skewed toward basal locations that have an earlier onset of cochlear degeneration.

A similar analysis of the structural correlates of 8-

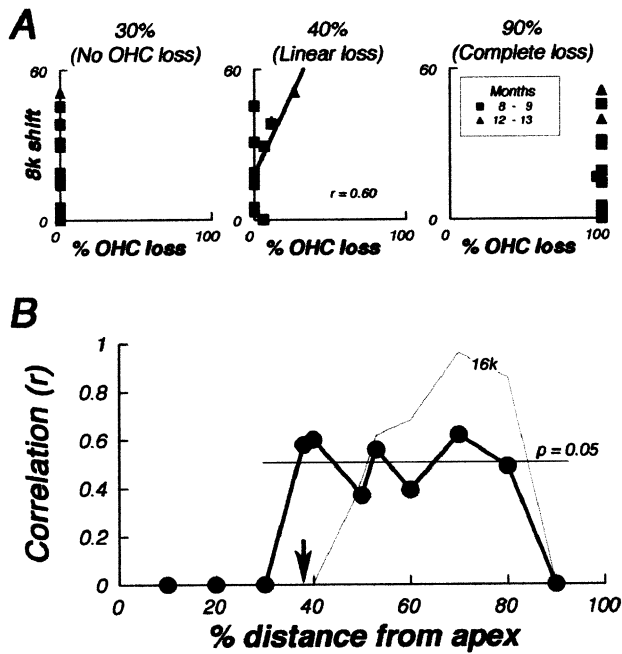


Fig. 6. Effects of regionalized OHC loss on the detection of 8-kHz tones. The horizontal line in B indicates the minimum statistically significant correlation coefficient ( $P=0.05$ ,  $n=12$ ). The arrow points to the expected transduction site for 8-kHz stimuli. Additional plotting conventions are described in Fig. 5.

kHz hearing loss is presented in Fig. 6. Expanding on results that are shown in Fig. 5, this larger sample of middle-age mice showed little OHC loss in the apical 30% of the cochlear partition (Fig. 6A). The progressive nature of the hearing loss was confirmed by an increase in missing OHCs at the 40% location, particularly among old mice.

Results at the 40% location suggest a dichotomy between middle-age and old mice with 8-kHz threshold shifts. Middle-age mice with 30 dB or more threshold shifts frequently showed no OHC loss. This lack of overt degeneration points out the importance of the more subtle cellular changes that contribute to auditory dysfunction prior to cell death. In spite of the limitations of OHC counting methods, the combined data from both age groups were fit by one statistically significant correlation ( $P<0.05$ ) and therefore identify this cochlear location as a potentially informative site for a more detailed histological assessment of the precursors of hearing loss.

The effects of cochlear location on 8-kHz correlation coefficients are summarized in Fig. 6B. Statistically significant correlations extended from basal locations of 70% to apical locations of 38%. In the context of the structure–function correlations of 16-kHz stimuli, these results imply the involvement of more apical locations in the 8-kHz threshold shifts. The apical limit of these regionalized effects corresponds well to Ehret's esti-

mates of the transduction site for 8-kHz stimuli (arrow).

#### 4. Discussion

Histological evaluations of OHC loss demonstrated systematic patterns of cochlear degeneration in the aging cochlea. These structural changes were well correlated with the contemporary status of auditory function in behaviorally characterized C57BL/6J mice, even though long-term psychophysical assessments indicated that the progression of hearing loss was episodic and highly variable within our subject group (Prosen et al., 2003). These results suggest that mice show differences in the absolute timing of regionalized OHC loss but not the sequence of degenerative effects that are associated with functional deficits. An important implication of these findings is that mice of different chronological ages can be matched in terms of 'functional age' to isolate the site and anatomical expression of ongoing cochlear pathology. The sensitivity of behavioral methods to early hearing deficits, particularly when tests are conducted in the presence of background noise, opens the possibility for functionally directed anatomical investigations into the ultrastructural and metabolic precursors of deafness that occur well before overt OHC loss.

The histological assessments of the present study have emphasized correlations between OHC loss and hearing impairment. A similar analysis was performed on inner hair cells (IHCs). As noted for OHCs, the number of surviving IHCs declined precipitously in the basal cochlea of middle-age mice. A less organized pattern of degeneration was noted as hearing loss progressed to the apical cochlea of old mice. Instead of an advancing regionalized loss, a uniform 20% reduction of IHCs was observed. Neither the magnitude nor location of this more diffuse pathology was correlated with OHC survival patterns or behavioral threshold shifts.

##### 4.1. The 'functional age' of C57BL/6J mice

Comparisons of age-matched groups of C57BL/6J mice showed generalized trends toward total OHC loss with advancing age (Fig. 2A). On average, hair cell degeneration in young mice was limited to the most basal locations of the cochlear partition and encompassed increasingly apical locations in middle-age and old mice (Fig. 2B). Within a particular age group, individual subjects showed considerable variation in the location and extent of pathology (Fig. 3). Because this progressive hearing loss is age-related but not age-specific, important ambiguities arise from anatomical sur-

veys that are organized by the chronological age of C57BL/6J mice.

The prevalence of inter-subject variability within age-matched groups of mice does not preclude an orderly cochlear pathology. The magnitude of OHC loss was correlated with cochlear location in subjects of all ages (Fig. 4A). Similar correlations were observed for the location of OHC loss and the extent of behavioral threshold shifts among middle and old age mice (Fig. 4B,C). These results imply that specific patterns of OHC loss lead to systematic and predictable functional consequences.

Histological studies provide a single look at the structural correlates of age-related hearing loss within each subject. Individual differences in OHC survival rates make it difficult to capture critical events in the progression of hearing loss with anatomical sampling techniques that are based on chronological age. Alternatively, our results suggest that informative insights into the current status of cochlear degeneration can be gained by classifying subjects in terms of their performance in auditory psychophysical procedures, just as audiological assessments are commonly used to characterize human presbycusis. In its simplest application, this behavioral approach assigns a ‘functional age’ that is assumed to reflect generalized patterns of OHC loss or related pathologies.

Table 1 compares the broad chronological age groups of our anatomical study to the functional age groups proposed by Prosen et al. (2003). Psychophysical classification of C57BL/6J mice in functional age groups 1 and 2 was based on a heightened susceptibility to masking noise and elevated thresholds at higher frequencies (16 kHz). When the magnitude of these hearing deficits is related to regionalized OHC loss in Fig. 5, the resulting correlation suggests an edge of behaviorally relevant degeneration at a cochlear distance 50% from the apex. Current estimates of the cochlear frequency map for laboratory mice predict a similar transduction site for 16-kHz tones (Ehret, 1975; Ou et al., 2000).

The progression of behaviorally characterized hearing loss to functional age groups 3 and 4 is defined by threshold elevations in the 8-kHz frequency range. These mice contributed data to the structure–function correlations in Fig. 6. In spite of the considerable age

variation among these subjects (28–51 weeks), the magnitude of 8-kHz threshold shifts was correlated with ongoing OHC loss at a cochlear distance 38% from the apex. Again, these results correspond well to the predicted transduction site for 8-kHz tones in the mouse cochlea (Ehret, 1975; Ou et al., 2000).

Behavioral data (Prosen et al., 2003) suggest that the earliest indication of auditory dysfunction involves the instability of pure-tone thresholds in background noise. An age-related decline in auditory function in the presence of background noise is also a source of disability in human presbycusis (Lutman, 1991). The transduction mechanisms that allow the signal to be heard are especially vulnerable to localized pathology. Masking effects, however, are exacerbated by a loss of frequency selectivity that may be caused by regional metabolic changes or pathology at remote cochlear locations (Lyregaard, 1982; Matschke, 1991; Scharf, 1978). It may be possible to isolate the functional consequences of multiple degenerative effects by examining the anatomical status of the cochlea at early versus later stages in the progression of hearing loss. The behavioral results of the Prosen study define a window of opportunity for examining the neuroanatomical basis of increased masking sensitivity prior to significant changes in hearing thresholds. Overt OHC loss occurs too late in this progression to contribute directly to the onset of auditory dysfunction in noise, but our correlation techniques provide a useful method for predicting the cochlear regions that are likely to manifest the functionally relevant precursors of hair cell loss in young mice.

#### 4.2. The precursors of hair cell loss

The role of OHC loss in human presbycusis is controversial. Schuknecht (1994) observed correlations between auditory threshold shifts and the cytochocleogram only when hair cell loss was the primary pathology. No structural correlates were found in 25% of cases. Felder and Schrott-Fischer (1995) failed to find consistent relationships between threshold shifts and sensorineural degeneration in a broad survey of human temporal bones. This uncertainty in gross cochlear pathology has shifted the emphasis of clinical

Table 1  
Location of active OHC loss in the functional age groups of C57BL/6J mice

Functional age group	Structural age group	Location of active loss	Hearing sensitivity	
			16 kHz	8 kHz
–	young	90	normal	normal
1–2	middle	50	elevated	normal
3–4	middle, old	38	elevated	elevated

Location of active loss is specified as percent distance from the apex. Functional age groups are taken from Prosen et al. (2003).

research to molecular and subcellular precursors of OHC loss that may be more closely linked to functional deficits.

Age-related changes in endolymph homeostasis and endocochlear potential due to atrophy of the stria vascularis have also been implicated in age-related hearing loss in gerbils (Gratton et al., 1996) and humans (Schuknecht and Gacek, 1993). Along similar lines of reasoning, Hequembourg and Liberman (2001) have argued that the loss of type IV fibrocytes in the spiral ligament is a primary degenerative event leading to ABR threshold elevation in the C57BL/6J mouse. The loss of these cells degrades the endocochlear potential by interrupting the normal cycling of potassium ions between the stria vascularis and the endolymphatic space. The early onset of elevated noise masking effects in the Prosen study corresponds well with the timing of fibrocyte degeneration (Hequembourg and Liberman, 2001). Moreover, in a manner reminiscent of Meniere's disease, the ensuing fluctuations of endolymphatic homeostasis may contribute to episodic variations of behavioral thresholds in noise.

Other pathological processes may impair signal transduction through more localized changes in OHC function. For example, a progressive disorganization of intracellular actin has been demonstrated in the OHCs of aging C57BL/6J mice, but not in a CBA strain that is known to maintain normal hearing (Hultcrantz and Li, 1995). This deterioration in the structural framework of OHCs is likely to compromise the active mechanical properties of the cochlea that enhance sensitivity and frequency tuning in normal listeners.

As clinicians and scientists develop more sophisticated tools for evaluating the molecular biology of the aging cochlea, mice are certain to remain a preferred context for laboratory studies of presbycusis. Our current investigations have supported the utility of the C57BL/6J strain by confirming a progression of hearing loss that captures the essential perceptual behaviors and cochlear anatomy of the human condition. More importantly, our correlation techniques have begun to characterize this important animal model in terms of functional age groups that link specific perceptual deficits to ongoing regionalized pathologies. Our analyses have focused on OHC loss, but these findings offer a new approach for bringing a functional perspective to any structural evaluation of the cochlea.

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