Chapter 4
Closing the Gap Between Neurobiology and Human Presbycusis: Behavioral and Evoked Potential Studies of Age-Related Hearing Loss in Animal Models and in Humans

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4.1 Introduction

4.1.1 Contributions of Animal Models to Understanding Human Presbycusis

Any reader who has grown up with a pet dog cannot have failed to notice that the effects of advancing age in dogs are not very different from those apparent in aging grandparents, except that in calendar time they appear more rapidly. Although domesticated animals may present a special case compared with wild animals that hardly survive to the age of sexual maturity, a few wild animals do survive and they also exhibit these common effects of human aging. Very close to human sympathies are the observations of elderly chimpanzees by naturalists who, having followed their stable groups for many years, write that the rare creature that has successfully survived the challenges of the wild exhibits the same thinning hair, slow movements, and sagging and wrinkled facial skin as the elderly human (Hill et al. 2001). And given the laboratory studies of hearing in old monkeys (Bennett et al. 1983) and examinations of cochlear pathology in postmortem studies of aged pet dogs

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S. Gordon-Salant et al. (eds.), *The Aging Auditory System*,
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(Shimada et al. 1998), this wrinkled and slowly moving chimpanzee and the graying and arthritic dear old pet must both suffer from poor hearing as do elderly humans.

This chapter is focused on the experimental evidence that will more definitively characterize age-related hearing loss (ARHL) in animals in comparison to human listeners. Both behavioral and noninvasive auditory evoked potential results (AEPs) are included, the latter so that animal data can be assessed relative to human data in very similar experimental paradigms. These laboratory experiments have most often had their rationale founded in the data either from audiology practice and psychophysical laboratory research with human listeners or from neurobiological findings of age-related changes in anatomical structure and connectivity, neurochemical and genetic expression, and physiological evidence observed in laboratory animals. The task of this chapter is to mediate between these separate disciplines. These functional studies of behavior and AEFs in old animals can provide a means of testing hypotheses about presbycusis that are not readily tested in the two flanking disciplines. They cannot be tested in the human psychophysical laboratory because humans cannot be subjected to stringent environmental, surgical, or genetic manipulations, and neither can they be tested in the neurobiological laboratory because neurobiological end points, e.g., evidence of histopathology and loss of neurons or changes in genetic expression with increasing age, have no direct a priori connection to the phenomena of sensory experience. Thus the behavioral and AEP data obtained from noninvasive procedures, often in the awake and behaving animal and in the similarly awake and behaving human research participant, are intended to provide different links back and forth between age-related neurobiological changes in animals using invasive techniques on the one hand and sensory-perceptual measures obtained in human listeners on the other. It is the convergence of their outcomes with each other and with those obtained in clinical practice that will contribute to understanding the common features of presbycusis and their neurobiological bases.

Realistic models of the various features of human presbycusis that are based in animal behavior and neurobiology will become even more valuable in the future with their further evolution and with the continuing development of translational research programs. Besides achieving an integrated multidisciplinary understanding of presbycusis, the ultimate goal of the research on ARHL at each of these levels of analysis is to discover how this progressive deficit may be retarded or prevented or possibly reversed. These translational programs will almost certainly need to assess their validity in animal models of presbycusis before they are ready for clinical testing in humans.

4.1.2 Distinctions Between the Simple and the Complex in Signals and in Listening Environments

In most studies of human presbycusis, the investigators have focused on age-related changes in the audiogram, i.e., the loss of absolute sensitivity as given by the ability to detect pure tones in quiet, measured across the normal frequency range of hearing. In other experiments, subjects are asked to detect, identify, or respond to suprathreshold, clearly audible signals that may be simple tones or noise bursts, may consist of patterned sequences of stimuli that vary in their spectral content and intensity over time, or may contain fragments of speech or sentences, sometimes in complicated listening conditions that include competing messages or reverberation. These latter experiments variously simulate the characteristics of normal speech signals and the nonoptimal listening environments typical of everyday life. The basic finding in the first set of experiments is that absolute thresholds steadily increase with advancing age, and in the second set, that elderly human listeners are often less able than the young to detect or to identify signals when they are presented against a noisy or competing background, even though the signals and the background stimuli would all be audible if they were presented by themselves. Examples of these two types of experiments are shown in Fig. 4.1a (for simple stimuli) from a study by Allen and Eddins (2009) and Figure 4.1b (for complex stimuli) from a study on the effects of reverberation on speech perception published by Nabelek and Robinson (1982). Reduced performance with advancing age is apparent in both sets of data. The appearance of decrements in hearing ability as early as 30 to 40 years of age in these data and in other life-span studies of nonpatient populations such as those of Bergman et al. (1976) and Brant and Fozard (1990) indicate that hearing sensitivity and auditory processing apparently begin a gradual but significant progressive decline in middle-aged adults. Thus even though the word "presbycusis" was initially designed by Roosa (1885) to specifically label the clinically significant

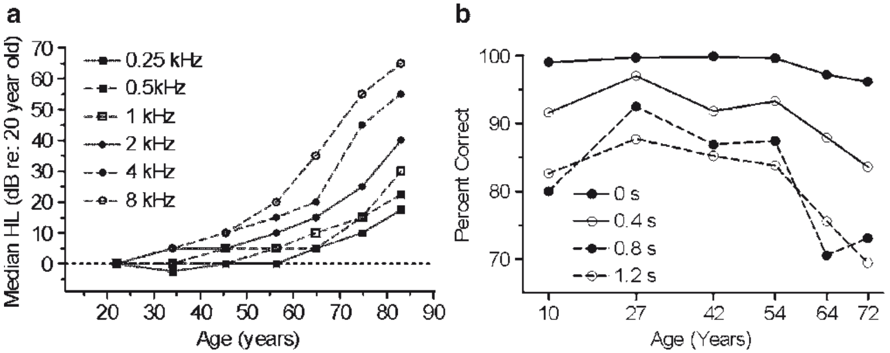

Fig. 4.1 (**a**) Age-related hearing loss (HL) across standard test frequencies from 250 Hz to 8 kHz between the ages of 20 to over 90 years (overall n = 1,209, 689 women, 520 men) presented as median absolute thresholds expressed relative to a group of subjects between the ages of 18 to 20 years (Eddins and Allen 2009). (**b**) Age-related changes in correct word identification presented monaurally in listening environments having different degrees of reverberation (i.e., differences in the duration of a series of diminishing echoes of the stimuli) from 0 to 1.2 s during and after the presentation of a stimulus (groups of 10 for each age group, 46 women, 14 men). (Adapted from Nabelek and Robinson 1982.)

hearing loss of elderly patients, these empirical data suggest the value of including intermediate middle-aged subjects, animals and humans alike, in laboratory studies, to identify and, one hopes, to understand and eventually learn to control the conditions that lead to early onset ARHL.

4.1.3 Chronological versus Biological Aging and Individual Differences in ARHL

A limitation of averaging group data across a time series is that the analysis cannot discriminate between an effect in which subjects are relatively homogeneous in their slow progression of hearing loss, or when each of the subjects displays a rapid increase in hearing loss for some particular frequency but differ in the age at which the deficit first appears. Indeed, all large-scale studies of ARHL have considerable scatter around the mean within an age group, and the distribution of individual differences is most often not a Gaussian distribution but is significantly skewed upward or downward depending on the test frequency and the age group. For example, in the group data depicted in Figure 4.1a, most middle-aged participants have a very small deficit compared with the young, but a few have a serious hearing loss more typical of the elderly. Also, the majority of elderly listeners have a serious hearing loss, especially for the higher test tones, but a few elderly participants have maintained a high level of sensitivity, close to that typical of the young listener. Hence, although increasing chronological (or "calendar") age is obviously associated with greater hearing loss in human listeners, as can be seen most persuasively in the comparison of the extreme age groups, the scatter within the intermediate age groups shows that its onset and progression are highly variable from person to person.

One recurring theme in this chapter is that these individual differences should not be ignored but instead be more thoroughly studied because understanding their biological and environmental bases may provide useful clues to the general properties of presbycusis. One source of the scatter within an age group is that beginning at ~40 to 50 years of age, women tend to have better high frequency thresholds (on the order of 5- to 10- dB) than men of the same age. This difference between men and women has been found in other large-scale studies (e.g., Pearson et al. 1995), and it is one of the findings that has been followed up in the animal laboratory but so far with mixed results. Henry (2004) found an advantage for female over male CBA mice but for male over female C57BL/6 mice; Guimaraes et al. (2004) found an advantage for female CBA mice but only in a group of senescent mice older than 2 years of age, not at the ages at which Henry (2004) had found the CBA female advantage; and Ison and Allen (2007) found no sex difference in large groups of CBA mice at all ages between 2 and 25 months of age when cohorts of males and females were balanced for time of testing.

Other factors that may be responsible for scatter within age groups of humans are variation in the cumulative effect of noise exposure across the life span, the increasing incidence of medical conditions that may affect hearing, variation in the reactions to the treatment for these conditions, dietary variables, and genetic differences that may directly impact hearing (van Eyken et al. 2007). Each of these isolated factors is now being investigated in the animal laboratory, and there is even one very interesting study of an interaction between early noise exposure and later ARHL by Kujawa and Liberman (2006); these investigators showed that an early noise exposure that had little immediate effect accelerated the progress of ARHL as assessed many months later. Other factors that influence ARHL may be similarly subtle and difficult to isolate because they too may interact in as yet unknown ways with other predispositions. For example, stable individual differences in the onset of hearing loss have been reported in inbred C57BL/6 mice (Ison et al. 2007) even though these mice have the same genetic background, were raised in the same controlled environment, and were even tested on the same day. However, it should also be noted that in this experiment, the within-strain variability of C57BL/6 mice was relatively small compared with the distribution of ARHL across populations of mice of different strains and different environmental conditions; i.e. genetic background and obvious environmental differences are responsible for much of the variability in mouse hearing.

Other researchers who work with large groups of human volunteers (e.g., Gates et al. 1999) have suggested that the differences not only in the time of onset of ARHL but also in the pattern of ARHL across spectral frequencies can be obscured in group data. These authors and others have provided data showing that the stereotypic profile of sharply increasing ARHL across frequency in the older age groups shown in Figure 4.1a may be characteristic of many but most certainly not all elderly listeners and, particularly, that many have a more serious low-frequency ARHL than the group data would suggest. To follow up these earlier observations, Allen and Eddins (2009) used an unbiased profile analysis of the data depicted in Figure 4.1a to partition the individuals into seven profiles that provided the best fit. They found that most participants, 80% of the men and 70% of the women, provided profiles that looked like an exaggeration of Figure 4.1a, with minimal ARHL for low-frequency test stimuli and a sharp rise for high frequencies, whereas the remaining participants were distinguished by their having relatively more severe ARHL for low-frequency test stimuli and then a less steep increase in ARHL for higher frequencies. This latter profile was apparent in 30% of the women and just 20% of the men, i.e., ~50% more common in women than in men. Jerger et al. (1993) similarly observed a more even pattern of ARHL across test frequencies in women than in men, in part because the women had a less severe loss for high frequencies but a more severe hearing loss at low frequencies. This latter effect was present in the Allen and Eddins data but was small and not significant. Past observation of this sex link between these two ARHL profiles has spurred attempts to determine their antecedents in the environment or in inherited or familial antecedents (Gates et al. 1999). The full treatment of this endeavor goes beyond the scope of this chapter, but it is clearly relevant to the general topic of animal models of ARHL.

4.2 Are There Different Types of Hearing Loss, Different in Origin and in their Effects?

4.2.1 The Psychophysical Question: Is ARHL Simply a Loss of Absolute Sensitivity?

One presently unresolved issue in interpreting the two manifestations of ARHL shown in Figure 4.1 is whether they have a single source in the loss of absolute sensitivity or, instead, whether the data presented in Figure 4.1b reflect at least a partially independent deficit in complex sensory processing and perception. Tremblay and Burkard (2007) describe experimental approaches that have been used in ARHL research with human listeners to isolate the loss of threshold sensitivity from a possibly additional effect of age on the efficacy of complex auditory processing. Some classic research strategies have been developed to address this issue with human listeners, but their extensive review of the data led them to conclude that as yet there is no single manipulation that cleanly separates the two types of hearing loss. One method is to assemble a single large group of elderly listeners and then subject them to a rigorous testing schedule (e.g. Humes et al. 1994; Humes 2005) in which their scores on the test battery are used to develop a pattern of correlations among them. Humes (2005) tested over 200 elderly listeners with standard clinical audiograms, brainstem AEPs, intelligence scales, several measures of complex auditory processing, including discrimination of tone duration and temporal order, and several measures of speech recognition. The variable that was most important in accounting for individual differences in speech recognition scores was hearing loss as revealed in the audiogram, whereas significant but relatively minor contributions were provided by IQ tests, differences in central processing, and age.

Another commonly used strategy is to compare two groups on some measure of auditory processing, one group of elderly listeners with so-called “golden ears” that have an unusually high sensitivity for at least the range of low- to mid-frequency test stimuli to be used in the experiment and so can be matched one-to-one with a second group of average young listeners (e.g., Snell 1997 for gap detection; Harris et al. 2008 for an evoked potential study of frequency discrimination). And last, two pairs of matched groups can be assembled, including two groups of young and elderly subjects with matched hearing sensitivity within the normal age plus two additional groups with carefully chosen “below average” young listeners with some degree of hearing loss that can be matched to elderly listeners with “average” hearing loss for their age. This classic “2 × 2” factorial design supports a type of statistical analysis that can separate out the independent contributions of hearing loss and of age and also assess the contribution of their interaction. Thus Gordon-Salant and Fitzgibbons (1995), in a study of advancing age and hearing loss on speech perception in reverberant environments with variously time-distorted speech signals, reported that both hearing loss and age have independent effects on performance and that the effect of age increased with the increasing degree of distortion in the stimuli.

This same confounding of age and loss of absolute sensitivity is present in the animal laboratory, and the few experiments that have explicitly recognized the problem have resolved it using the same tools as in the human laboratory, to find similar outcomes. For example, May et al. (2006) found in a longitudinal behavioral study in mice that individual differences in the decline of frequency selectivity with increasing age did not covary with their loss of absolute sensitivity; i.e., age had an independent effect on performance. Barsz et al. (2002) reported that the individual differences in the loss of temporal acuity in a behavioral gap-detection study with aging mice were correlated not only with hearing loss but also with advancing age independent of hearing loss. And Walton and his colleagues found in an electrophysiological study of temporal acuity that the near-senescent CBA mice was impaired compared with young mice (Walton et al. 1998), whereas temporal acuity was not impaired in middle-aged C57BL/6 mice that had more hearing loss than old CBA mice (Walton et al. 2008). All of these researchers cited above have concluded that the effects of age on complex auditory processing are greater than would be expected just on the basis of age-related changes in audibility. Further converging support for this position is provided in neurobiological evidence of histopathology at both peripheral and central sites within the auditory system.

4.2.2 Neurobiology: Might the Type of ARHL Differ According to the Site of the Pathology?

Structural deterioration in the ear has been observed in all animal models of aging and also in humans in temporal bone histopathology in postmortem specimens (Schmiedt, Chapter 2). For example, changes in vascularity and in supporting structures and sensory-neural elements within the cochlea have been reported in humans (Johnsson and Hawkins 1972; Nelson and Hinojosa 2006) and in a great variety of laboratory and domesticated animals (e.g., rats, Keithley and Feldman 1982; rhesus monkeys, Hawkins et al. 1985; squirrel monkeys, Dayal and Bhattacharyya 1986; chinchillas, Bohne et al. 1990; gerbils, Gratton and Schulte 1995; mice, Spongr et al. 1997; Ichimiya et al. 2000; Hequembourg and Liberman 2001; dogs, Shimada et al. 1998; guinea pigs, Ingham et al. 1999). Such peripheral deterioration might be conceived as resulting only in a loss of absolute sensitivity, but it has been suggested that it may also have a direct effect on central processing because it alters the quality of the neural information that is transmitted to the brain through the auditory nerve. Hellstrom and Schmiedt (1991) suggest that peripheral sensory damage could result in a loss of synchrony in spiral ganglion firing and thus indirectly influence central neural processing even in the absence of direct age-related deterioration in the central auditory nervous system (CANS). This is an important and plausible hypothesis, but there is as yet no direct evidence that advancing age reduces auditory nerve synchrony as measured, e.g., in the degree of jitter in its input to the cochlear nucleus.

There is also abundant evidence for the presence of pathological changes in the auditory cortex, midbrain, and brainstem with advancing age (Canlon and Walton, Chapter 3). Changes in the human brain are apparent in postmortem studies; these are reviewed by Mrak et al. (1997). These authors describe the presence of gross changes in the size of the brain, number of cells, and dendritic fields and by more subtle changes in major neurotransmitters in the cholinergic, dopaminergic, serotonergic, and adrenergic systems. The more recent studies using in vivo noninvasive imaging have but very rarely touched on the auditory system; one relevant report (Lutz et al. 2007) found changes in Heschl's gyrus that suggested a disruption of fiber tracts and changes in the inferior colliculus (IC) but no changes in either the lateral lemniscus or the medial geniculate. In the animal laboratory, changes in vascular support structures have been reported in the medial trapezoid body of the auditory brainstem in old rats (Casey and Feldman 1985), and changes in synaptic connectivity have been reported at every level of the auditory system, in the auditory cortex (Vaughn 1977), in the IC (Helfert et al. 1999), in the superior olivary complex (Casey 1990), and in the cochlear nucleus (Helfert et al. 2003). There is also evidence provided by Zettel et al. (2007) that with advancing age in the mouse, there is less expression of potassium ion channels expressed by the *Kcnc1* gene in the medial nucleus of the CBA trapezoid body, an effect that may be related to deficits in downstream control over cochlear sensitivity that these authors found in *Kcnc1* null mutant transgenic mice. Furthermore, in the adult cat, there is evidence that synchrony at the level of the trapezoid body is greater than that provided by the auditory nerve to the cochlear nucleus, this being a beneficial result of central neural processing (Joris et al. 1994). There is as yet no evidence that such enhancement of synchrony by brainstem neural processing deteriorates with age, but the changes in the expression of potassium ion channels in the trapezoid body of the old mouse observed by Zettel et al. (2007) is consistent with this hypothesis.

4.2.3 Peripheral Hearing Loss Can Alter Both the CANS and Central Auditory Processing

There is a significant literature on the degree to which changes in the central auditory system with advancing age may in some cases be directly mediated by peripheral pathology and in other cases by increasing age alone. Most of our understanding of this phenomenon is the product of an extensive program of research conducted over the years by Willott and his colleagues that analyzed the relationships between increasing age, the time course of histopathology, and associated changes in neural activity in CBA and in C57BL/6 mice (reviewed in Willott 1996). For example, cell loss in the high-frequency regions of the anterior ventral cochlear nucleus occurs at ~7 months of age in the C57BL/6 mouse after peripheral hearing loss but not until 2 years of age in the CBA mouse (Willott et al. 1987). In contrast, the loss of octopus cells in the posterior ventral cochlear nucleus becomes apparent in C57BL/6 mice at the same age that it is observed in CBA mice, when the mice are ~2 years old (Willott and Bross 1990). Another very important finding is that the tonotopic maps of the IC (Willott 1986) and the auditory cortex (Willott et al. 1993) are profoundly changed with increasing hearing loss in middle-aged C57BL/6, so that formerly high-frequency areas of these brain regions come to respond with great sensitivity to low-frequency stimuli. This electrophysiological sign of a more extensive representation of low frequencies in the middle-aged C57BL/6 mouse is accompanied by enhanced behavioral responsivity to these stimuli, as demonstrated, e.g., by Willott and Carlson (1995) and Ison et al. (2007).

4.2.4 Experimental Manipulations at Different Sites Can Produce Different Types of Hearing Loss

4.2.4.1 Manipulating the Integrity of the Cochlea

There is considerable evidence for extensive structural degeneration in the ear and the brain in all the animal models of aging that is confirmed in the available human evidence, but it must also be noted that most of these data are scattered across different species, and it is rare that different histopathological end points and functional measures are obtained in the same individual. And even at best, this evidence is correlational. For example, one very interesting set of findings by Kazee et al. (1995) is that regional loss of hair cells along the basilar membrane of the aging C57BL/6 mouse is associated with a frequency-specific increase in auditory thresholds and also with a loss of synaptic endings through the central nucleus of the IC. Although these observations are important, there is no direct evidence that these observations have uncovered a causal chain in which hair cell loss is the primary effective agent that leads directly to the rise in thresholds and hence to the loss of synapses in the IC. The search for causality is the rationale for trying to simulate some effects of age in young animals by directly producing structural or neurochemical changes in the auditory system and then determining the chain of effects of these manipulations.

A study that appears to simulate the effects of aging on regional hair cell loss in the cochlea and thus at least ties hair cell loss causally with absolute threshold changes was provided by Prosen and Moody (1991). These researchers trained young adult chinchillas in which one cochlea had been surgically destroyed to press a lever when test tones were presented, and training continued until the animals were able to generate stable, absolute, and differential thresholds across their range of hearing. Then the researchers destroyed just the apical (low-frequency) hair cells in the remaining cochlea of four of these chinchillas by freezing the area with a cryoprobe. The restricted effect of this manipulation on apical hair cells was later verified in a histopathological study, while the functional effect of the manipulation was assessed by the within-subject changes in behavioral thresholds that resulted after the second surgery, in quiet or in the presence of a high-pass masking noise. As could be expected given the known distribution of best frequencies along the basilar membrane, both the absolute and differential thresholds for low- but not high-frequency test stimuli were increased by apical hair cell loss. However, the animals could still detect these low-frequency stimuli when they were presented at higher levels, and, to a limited extent, the animals were able to discriminate between different low-frequency test tones. An important additional finding was that high-frequency masking stimuli further reduced low-frequency hearing, an indication that the residual low-frequency sensitivity is mediated in part by more basal high-frequency regions of the cochlea. This finding agrees with the spread of excitation and receptivity of high-frequency hair cells in the basal areas of the cochlea to relatively intense low-frequency test stimuli reported by Cody and Russell (1987). It may also explain the common observation that there is not a simple one-to-one relationship between the position of a hair cell along the basilar membrane and its sensitivity to particular tonal stimuli, especially at high stimulus levels. It would also have been interesting to see if this manipulation would have changed the patterns of connectivity with the IC as has been observed in the C57BL/6 mouse.

The most recent method of manipulating the auditory periphery is by genetic engineering focused on specific stages of sensory processing in the ear. McCullough and Tempel (2004) studied the effects of deleting several related alleles of the gene that encodes the protein that is responsible for extruding calcium from stereocilia and spiral ligament cells (plasma membrane calcium ATPase isoform 2 [PMCA2]). They discovered that these different alleles produced phenotypes with varied degrees of hearing loss appearing in ABR thresholds at different onset times. These data certainly demonstrate the causal relationship between hair cell dysfunction and ABR thresholds and further raise the possibility that one cause of ARHL may result from a changing expression of PMCA2 with advancing age.

4.2.4.2 Manipulating the Central Auditory Nervous System

There are other reports that specific experimental administration of drugs or destruction of regions within the CANS can have substantial specific sensory-perceptual effects that are at least qualitatively similar to some aging effects. For example, scopolamine is a cholinergic antagonist best known in behavioral pharmacology for its deleterious effects on memory, but it has also been shown that the systemic administration of scopolamine adversely affects gap-detection measures of temporal acuity in human volunteers (Caine et al. 1981) and in rats (Ison and Bowen 2000). However, it does not affect absolute threshold sensitivity. Intracranial application of another cholinergic antagonist (atropine) directly onto the cochlear nucleus of cats increased the threshold at which these subjects could successfully perform a behavioral task in which tones were presented in noise (Pickles and Comis 1973). It is also important that this manipulation had little effect on responses to tones presented in quiet. Turning to another neurochemical manipulation, vigabatrin is a pharmacological compound that prevents the breakdown of GABA in the synaptic cleft and has been used clinically to alleviate epilepsy. Gleich et al. (2003) found a dose-sensitive enhancement of behavioral gap-detection thresholds by systemic administration of vigabatrin in old gerbils with unusually poor temporal sensitivity before drug treatment, suggesting an important role for GABA in this task. It has also been shown that temporal acuity as measured by gap detection is very much diminished by bilateral lesions of the auditory cortex in human patients after vascular accidents (Buchtel and Stewart 1989) and in rats after surgery (Bowen et al. 2003). These lesions also did not affect absolute thresholds. And furthermore, there are reports (e.g., Kopp-Scheinpflug et al. 2003) that neurons of the medial nucleus of the trapezoid body in *Kcna1* transgenic mice that lack the Kv1.1 ion channel show deficits in onset responding that would certainly degrade the neuronal synchrony of firing in this nucleus. There are no changes in absolute threshold in the null mutant mice. However, these same null mutant mice, like old mice, also have behavioral deficits in sound localization (Allen et al. 2003), which is in part mediated by the trapezoid body.

These experimental data show in both adult humans and laboratory animals that threshold sensitivity and frequency discriminations depend on the integrity of peripheral auditory structures and that the integrity of central neural and neurochemical mechanisms is necessary for complex auditory processing but does not affect absolute threshold measures. They show, at a minimum, that altering the integrity of these structures does affect hearing, but they do not speak to the degree that, e.g., blocking cholinergic receptors by scopolamine simulates an age-related loss of cholinergic neurons or changes in the sensitivity of cholinergic receptors. These experimental data also suggest the possibility that age-related central processing deficits may take a number of different forms depending on where deterioration has occurred in the CANS. For the periphery, there are arguments that hearing loss attendant on stria vascularis dysfunction has a fundamentally different functional signature than does hair cell loss (Boettcher 2002). It is no less plausible to suspect that the anatomical targets of aging could vary among individuals, and if so, it is then conceivable that some elderly listeners could have a deficit only in the functions mediated by specific sites, such as spatial localization mediated by the nuclei of the superior olivary complex, but not in functions mediated by octopus cells in the cochlear nucleus, perhaps gap detection. Although it may seem more likely that the central degenerative effects of aging would appear consistently throughout the CANS rather than being restricted to one nucleus or another, this is an idea that has never been tested. It is possible that physiological/gene-expression examinations of the CANS carefully combined with the results of a battery of auditory tasks tests would provide a useful test of this hypothesis.

4.3 Noninvasive Objective Methods for Studying ARHL in Animals and Humans

4.3.1 Introduction to the Methods

This section provides a closer examination of the nonverbal behavioral and noninvasive AEP methods that have been used in both animal and human research. Following the earlier organization, the first part deals with age-related changes in absolute thresholds related to Figure 4.1A, and the second examines changes in suprathreshold hearing, including both high-intensity simple test stimuli and the more complex hearing paradigms related to Figure 4.1B.

Psychoacoustic and audiological investigations rely on the willingness of research subjects to follow instructions and indicate that they heard a stimulus by making some voluntary response, such as pressing a button or pointing to a location. The experimenter's careful control over the stimulus conditions ensures that the subject is listening for the intended stimuli. Elaborate statistical analyses are used to convert the responses into a single measure of sensitivity, these being complicated because even cooperative human volunteers will fail to respond to stimuli that were previously detected (a miss) or will report hearing a sound when there was none presented (a false alarm) and, at worst, human research participants sometimes appear to lose interest in the task at hand and may even fall asleep.

Each of these problems is magnified in animal research, beginning with the necessity of developing an indicator response that is sensitive to stimulus presentation. Procedures for measuring stimulus-evoked overt responding in the awake animal have all been developed over the course of about the last 100 years, starting with work by Yerkes on hearing in frogs (1905) and mice (1907). Some indicator responses are directly elicited by auditory stimuli as a built-in reflexive reaction to an acoustic stimulus, such as the Preyer reflex (studied in mice by Jero et al. 2001). Others are obtained by the modification of a reflex response by an auditory stimulus that has no built-in relationship to the response, this being an example of the prepulse inhibition phenomenon common to many reflexes and many species; its use in developmental and comparative sensory research has been described by Hoffman and Ison (1992). A third behavioral approach requires training the animal to make some more-or-less arbitrary response when an acoustic stimulus is presented and to refrain from responding in its absence. These training methods have been described, e.g., by Stebbins (1990) and Heffner et al. (2006), and their many contributions to auditory processing in animals have been described by Fay (1988) and Long (1994). The experiments by Pickles and Comis (1973) and Prosen and Moody (1991) cited above used training procedures, the experiments by Willott and Carlson (1995), Bowen et al. (2003), and Ison and Bowen (2000) used a prepulse inhibition paradigm, and the results of Ison et al. (2007) used the method of reflex elicitation.

Noninvasive electrophysiological responses that are evoked by auditory stimuli and now often used in both human and animal studies of hearing have evolved over the course of the last 40 years, beginning with the demonstration by Jewett et al. (1970) that very small bioelectric potentials can be measured with surface electrodes in response to simple acoustic pulses. (This is most often called the ABR). Similar methods have been refined so that AEPs and neuromagnetic auditory evoked fields (AEFs) can be recorded not only to simple tone bursts in experiments intended to measure absolute thresholds in animals and in human infants too young to cooperate with the audiologist but also to examine the physiological reactions to complex stimuli such as speech signals (Tremblay et al. 2002) and interaural timing cues (Ross et al. 2007). Most commonly, AEPs are collected when animals are anesthetized rather than awake, while in convenient contrast, adult human research participants can be awake and infants can be asleep. Depending on the stimulus paradigm, brain activity can be measured while participants are actively engaged in a listening task or, in contrast, passively exposed to the ongoing stimuli. Because of the different variations in AEP methods, it is possible to measure the physiological capacity of the human listener and animals either independent of the cognitive and emotional contributions to a behavioral response or dependent on these internal states, so as to conform to the needs of the experiment.

4.3.2 The Application of These Methods to the Study of ARHL

As described above, the most rapid behavioral technique to study hearing in animals is to take advantage of a built-in reflexive response to an abrupt and relatively intense sound burst, e.g., the rapid twitch of the ears that is called the Preyer reflex or the whole body startle reflex. Jero et al. (2001) measured the startle reflex in a group of young adult albino mice of the FVB strain that have substantial individual differences in hearing ability to determine whether startle elicitation could be used as a fast screening test of hearing. The startle reflex was recorded as "positive" or "negative" depending on a mouse making at least two visible startle responses to three presentations of either hand claps or the sound of two hammers hitting together and validated these scores against ABR click thresholds. They reported that the reflex test was successful in detecting all mice with a severe hearing loss, defined as an ABR threshold over 80 dB. The amplitude of the acoustic startle reflex (ASR) declines with age in humans as shown by Ford et al. (1995) in a study comparing two groups of subjects, one with a mean age of 22 years, the second a mean of 69 years. They also found that two components of AEPs evoked by startle stimuli were reduced in amplitude in the older subjects, N1 with a latency of 50 to 150 ms and P3 with a latency of ~300 to 600 ms. Similar declines in the ASR have been observed in old rats (Krauter et al. 1981) and in three strains of mice, with the time course of the decline in the ASR corresponding to the time course of their developing hearing loss as measured by ABRs (Ison et al. 2008). However, age-related decrements in reflex strength by themselves do not necessarily implicate changes in auditory function without converging evidence from sensory threshold measurements because the motor system loses motor axons and muscle fibers with increasing age (Einsiedel and Luff 1992). And furthermore, at least in the middle-aged C57BL/6 mouse, hearing loss for high-frequency test stimuli as shown in ABR measures is correlated with exaggerated startle reflexes for low-frequency stimuli (Ison et al. 2007); this is thought to be a result of central tonotopic reorganization as described by Willott (1996).

Behavioral measures of absolute thresholds in trained animals often provide measures that rival the sensitivity of human psychophysical procedures. Fig. 4.2 shows absolute thresholds obtained for young adult human listeners using the verbal instructions standard in clinical audiology (data kindly provided by David Eddins) and by adult laboratory animals: monkeys (Bennett et al. 1983),

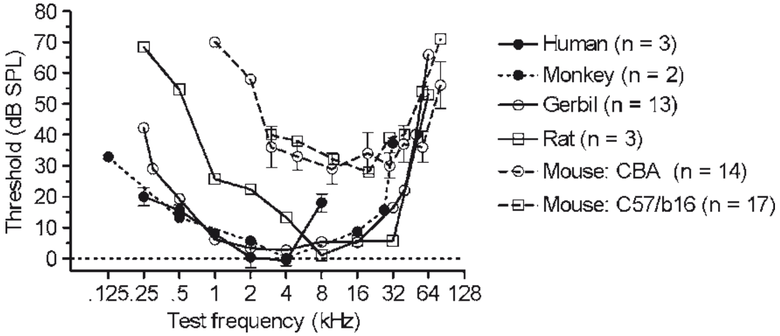

Fig. 4.2 Absolute thresholds obtained by the standard methods of clinical audiometry in young adult human listeners and by operant conditioning techniques in monkeys, gerbils, rats, and two mouse strains. (Animal data replotted from data in Fay 1988; human data kindly provided by David Eddins.)

gerbils (Ryan 1976), rats (Kelly and Masterton 1977), CBA mice (Birch et al. 1968), and from the same laboratory, C57BL/6 mice (Mikaelian et al. 1974). All of these studies used training techniques in which the animals either worked for food or escaped shock, with the acoustic stimuli signaling the availability of food or predicting the presence of shock. The standard mammalian U-shaped audiogram is evident in these data, with greatest sensitivity in a mid-frequency region that differs across species but is correlated with the species-specific spectral frequency of their vocalization, then a progressive increase in thresholds for lower and higher frequencies. It may be noticed that humans, monkeys, rats, and gerbils all hear stimuli presented at ~0-dB SPL at their best frequency, whereas mice appear to have relatively poor sensitivity. This difference could indicate that mice have a species-specific hearing impairment, but the real problem may have been that the training/testing method was still being developed at that time and was not yet well suited for these mice. Birch et al. (1968) described the mice as spending much of their time grooming (a classic displacement activity in response to conflict; Spruijt et al. 1992) and that when they were grooming, they did not respond to the tones.

Two behavioral experiments have followed changes in absolute thresholds across the adult life span (Mikaelian et al. 1974 in C57BL/6 mice; Bennett et al. 1983 in rhesus monkeys). Mikaelian et al. (1974) used the same methods as Birch et al. (1968) but tested their C57BL/6 mice for many months. The results of these two experiments are presented in Fig. 4.3. Both show a profound effect of advancing age on auditory thresholds, and both exhibit the sharply rising hearing loss for high frequencies, with more modest loss at low frequencies. Mikaelian et al. (1974) documented the increasing cochlear damage in his mice by sacrificing small numbers of mice at various time points to show how the behavioral changes corresponded to pathological changes in the ear. The monkeys tested by Bennett et al. (1983) were a subset from a group that were later sacrificed for an anatomical study that showed increasing cochlear damage in older animals (Hawkins et al. 1985). Unfortunately, the potential for studying the association of the individual differences depicted in the functional

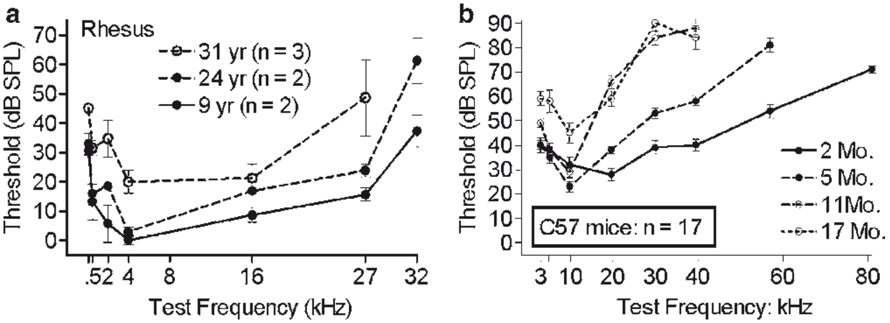

Fig. 4.3 Changes in auditory thresholds as a function of frequency of the test stimulus and age in rhesus monkeys (**a**; replotted from Bennett et al. 1983) and C57BL/6 mice (**b**; replotted from Mikaelian et al. 1974). The mice were also tested at other ages, omitted here for the sake of clarity.

data provided by Bennett et al. (1983) with the individual differences in the cochleograms reported by Hawkins et al. (1985) seems not to have attracted attention. It is important to note that the over all profile of these two sets of behavioral data was similar to that shown for humans in Figure 4.1a, as was the cochlea pathology in old animals similar to those found in temporal bones from elderly humans.

A major obstacle to the greater use of training methods for assessing auditory thresholds in older animals has been the prolonged investment in training the animal to do the task so that it is best employed in life span experiments for which animals can be trained and then tested many times over with increasing age (Mikaelian et al. 1974; Brown 1984; May et al. 2006). In contrast, the ABR measures are much more efficient, so that the entire spectrum of hearing in an anesthetized animal can be collected in ~1 hour. The validity of the ABR measures is shown in their providing an audiogram that has the same shape as the behavioral audiogram, save often for a constant offset that probably reflects the fact that behavioral thresholds benefit from greater temporal integration because behavioral test stimuli have a longer duration than ABR test stimuli. In general, ABR thresholds across species are near identical in their region of best sensitivity; this confirms the hypothesis that the higher behavioral thresholds of mice compared with those in gerbils and rats seen in Figure 4.2 resulted because it was difficult to control competing grooming behavior of the mouse, not because the mice were normally insensitive to sound. Fig. 4.4 shows ARHL for absolute thresholds measured by the ABR across age and across frequency in three laboratory animals commonly used in hearing research, the C57BL/6 mouse (adapted from Ison et al. 2007), the CBA mouse (adapted from Rivoli et al. 2005), and the Mongolian gerbil (adapted from Mills et al. 1990). The C57BL/6 and CBA mice obviously present very different profiles of ARHL. As noted in the behavioral data of Mikaelian et al. (1974) presented in Fig. 4.3, C57BL/6 mice undergo a progressive high-frequency hearing loss, but CBA mice have only a modest 10-dB hearing loss up to 20 months of age and then an additional 5- to 10-dB loss as the mice approach their median life span at ~24 months of age. The small frequency dependence of the hearing loss for the CBA mice is seen in the

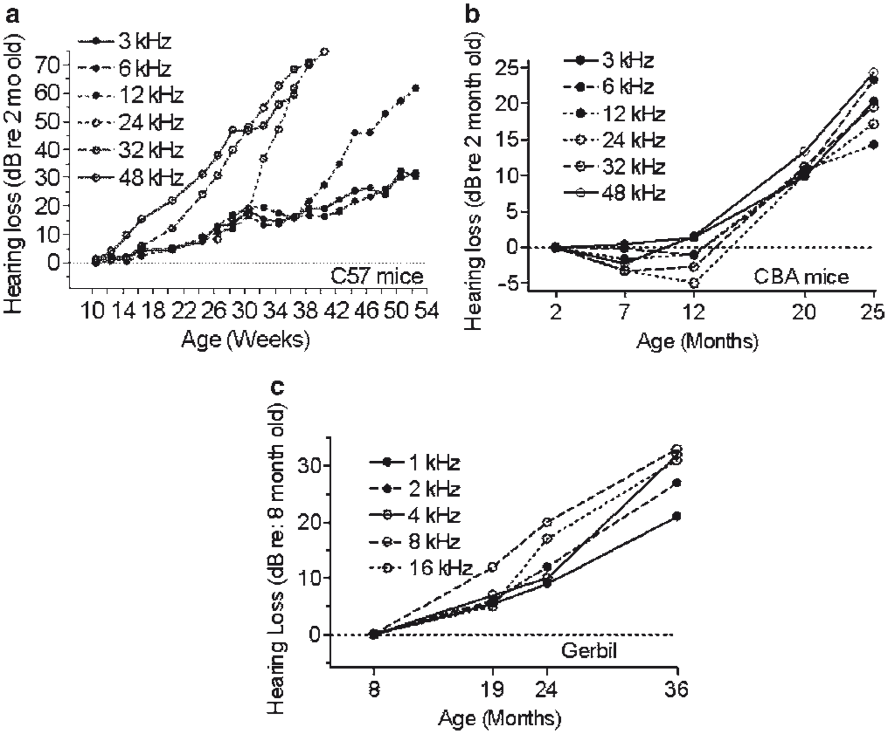

Fig. 4.4 Hearing loss with advancing age provided by changes in auditory brainstem response thresholds across frequency. (**a**) Longitudinal study of the C57 mouse (replotted from Ison et al. 2007). (**b**) Cross-sectional study of the CBA mouse (replotted from Rivoli et al. 2005). (**c**) Cross-sectional study of the gerbil (replotted from Mills et al. 1990).

comparison of the only slightly greater threshold loss for high- and low-frequency hearing compared with mid-frequencies. Erway et al. (1993) examined the ABR for 5 inbred mouse strains and all 10 of the F1 hybrid mice at different ages and found that the CBA mice had none of the three recessive alleles that lead to early ARHL, whereas the C57BL/6 mice had one such allele.

4.4 Peripheral Degeneration: A Major Source of ARHL in These Rodent Models

4.4.1 Cochlea Pathology and Its Relationship to Threshold Measures of ARHL

Spongr et al. (1997) provided quantitative measures of the patterns of hair cell loss in C57BL/6 and CBA mice that correspond with their disparate patterns of hearing loss evident in Figure 4.4. Hair cell loss began at the high-frequency base of the cochlea in the 3-month-old C57BL/6 mice, then progressed towards the low-frequency apex, whereas in the 18-month-old CBA mice, there was little evidence of hair cell loss, and at 25 months, hair cell loss was largely confined to the base and to the apex. Hearing loss in the gerbil was similar to that of the CBA mouse in its modest extent compared with the C57BL/6 mouse but had more definite monotonic frequency dependence than that of the CBA mouse, with 10 dB separating their best hearing at the lowest frequency of 1 kHz from the highest at 16 kHz (Mills et al. 1990). This seemingly "high-frequency" test stimulus of 16 kHz is still in the broad range of best hearing in the gerbil (see Fig. 4.2), and so this experiment may be thought to have missed any more serious impairment for higher-frequency hearing in these animals. However, Henry et al. (1980) tested gerbils up to frequencies of 64 kHz (but only up to 2 years of age) and did not find additional evidence of ARHL at high frequencies.

Tarnowski et al. (1991) tested ARHL in gerbils from the same colony used by Mills et al. (1990) and examined both hair cell loss and compound action potentials in the auditory nerve (roughly equivalent to wave I of the ABR) of young adult and 3-year-old gerbils. The old gerbils had variable hearing loss, but as a group, the hearing loss was relatively flat at ~20 dB for 4 kHz and below, with a further increase in hearing loss of ~10 dB for the higher frequencies. Unlike the C57BL/6 mouse (Spongr et al. 1997), the domestic dog (Shimada et al. 1998), or the monkey (Hawkins et al. 1985) but more like the CBA mouse (Spongr et al. 1997) and the guinea pig (Ingham et al. 1999), the old gerbil had its hair cell loss most pronounced at the apex, then next at the base, and only modest loss in the middle turns. Tarnowski et al. (1991) reported that although there was no precise correspondence between the frequencies that were lost with age and the regional hair cell loss as there was in the C57BL/6 and CBA mice, the overall loss of hearing across individuals was correlated with their overall loss of hair cells. Later studies by this group confirmed the conclusion of Tarnowski et al. (1991) that age-related degenerative changes in the stria vascularis were primarily responsible for hearing loss in the gerbil (Schulte and Schmiedt 1992). Schmiedt (1993) showed that strial degeneration in the old gerbil produced a reduction in the endocochlear potential (EP), which serves as the electrochemical "battery" for outer hair cell (OHC) activity. He concluded that the reduction in the EP was responsible for reduced OHC activity in response to acoustic input, which in turn reduced sensory-neural activity in the inner hair cells and thus activity in the auditory nerve (see Schmiedt, Chapter 2, for further details).

In contrast to the gerbil, the EP of the C57BL/6 mouse does not change over the period of rapid hearing loss (Lang et al. 2002; Ohlemiller et al. 2006), although McCulloch and Tempel (2004) suggest that changing the ionic composition of the EP may also impair its function. And although the C57BL/6 mouse appears to provide a very different animal model than the gerbil in its most obvious faster onset and greater severity of high-frequency hearing loss as shown in Fig. 4.4, these ABR threshold data indicate the middle-aged C57BL/6 mouse appears to present the two developmental profiles simultaneously, so that the slow rate of development of ARHL for relatively low-frequency test stimuli gives way progressively to the high rate of ARHL for the relatively high-frequency stimuli. Consistent with these observations, Hequembourg and Liberman (2001) found that there are two types of cochlear degeneration in the C57BL/6 mouse, one in the spiral ligament that is associated in time with a slowly developing non-frequency-specific hearing loss and a later degeneration of regional OHC loss that is associated with a more severe frequency-specific loss of hearing. Other investigators have also found degenerative changes in the stria vascularis of the C57BL/6 mouse (e.g., Ichimiya et al. 2000; Di Girolamo et al. 2001). Considering all these data, it may be very reasonable to use this mouse model to study simultaneously both common phenotypes of ARHL.

There is one other evoked response called an "otoacoustic emission" that is now the basis of a frequently used test of hearing in human infants and animal subjects. The test is based on the discovery by Kemp (1978) that weak sounds that originate in the inner ear can be recorded in the outer ear canal, with delays of several milliseconds after the presentation of an acoustic stimulus. These emissions are the result of an active increase in basilar membrane vibration as the OHCs contract and relax in phase with acoustic input, and their spectral frequencies as recorded in the outer ear canal include not simply the presented tone pips but also the frequency of the several distortion products produced by the OHCs. One particular large "distortion product otoacoustic emission" (DPOAE) is generated when two tones, f_1 and a higher f_2, are simultaneously presented, and the DPOAE has the frequency $[2f_1 - f_2]$. This is the DPOAE that is the primary focus of hearing tests because it is understood to be a valid index of OHC activity. Age-related declines in DPOAEs have been observed in older laboratory animals, most extensively by Jimenez et al. (1999) who measured DPOAEs in four mouse strains (including CBA and the C57BL/6) and showed the correspondence of these measures with the different degrees of susceptibility to ARHL of these mice. Guimaraes et al. (2004) observed that female CBA mice maintained better DPOAE levels with advancing age than males, even though their samples of male and female mice had no differences in ABR thresholds. Loss of DPOAEs has also been observed in middle-aged rhesus monkeys by Torre and Fowler (2000) and in middle-aged chinchillas by McFadden et al. (1997). The major benefits of DPOAE measures are that they measure OHC function in intact organisms, and in combination with the ABR, they provide an analysis of the relative contributions of OHCs, inner hair cells, and the auditory nerve fibers to ARHL. DPOAEs have also been studied in elderly human listeners, most often to find that the loss of absolute thresholds is primarily correlated with OHC loss (Oeken et al. 2000).

4.4.2 Suprathreshold Measures of ARHL

The ABR evoked by suprathreshold stimuli has been used to test the hypothesis that age and/or hearing loss alters central efficiency as measured by age-related changes in peak amplitude or in the latencies and interpeak intervals that are believed to represent ascending levels of brainstem processing. In their review of these data, Tremblay and Burkard (2007) conclude that these suprathreshold measures of amplitude and latency may be sensitive to age-related differences in peripheral sensitivity and central processing efficiency. One effect of a loss in audibility is a slowing of the first wave generated at the level of the auditory nerve, and the subsequent waves may be affected by both intrinsic central delays and by their being "inherited" from the auditory nerve. Central changes have been hypothesized to be more noticeable when very high rates of stimulation are used, much higher than the usual ABR rate of a constant 10–20 brief tone pips or clicks in each second. A special presentation pattern called the maximum length sequence (MLS) allows for very fast repetition rates in quasi-random sequences of brief stimuli interspersed with short periods of silence, so that linear effects (for isolated stimuli) or nonlinear effects (for dyads or triads of stimuli) can be recorded. Using MLS, Burkard and Sims (2001) were able to test subjects with modest hearing loss using click rates as high as 500/s and found that both wave I and wave V were delayed by ~0.1 ms in elderly subjects, with no age difference in the central delay between waves I and V.

A comparison of the age effects for a regular presentation ABR and a MLS ABR for click rates up to 250/s was provided by Lavoie et al (2008), with results again suggesting that ARHL can be observed in middle-aged humans. These investigators studied three groups of women: young women and girls, a young middle-aged group, and an elderly group with a range of just 44 to 62 years of age that was much younger than most elderly groups of subjects. This last group had only a small (but significant) hearing loss at 8 kHz compared with the youngest group. In the regular ABR, the oldest group showed a significant amplitude decrement on wave V compared with the younger groups (perhaps a sign of their small but real high-frequency hearing loss), whereas in the more rapid presentation of the MLS condition, the middle group had a smaller wave I compared with the youngest group. The authors also reported that the interval between the nonlinear waves I and V was longer for the oldest group compared with the middle group. Overall, these data support three conclusions: age effects on AEPs may be most apparent when the CANS is stressed by high repetition rates, central as well as peripheral processing is disrupted with age, and age effects can be observed in relatively young middle-aged listeners. A research program that repeated these age-sensitive MLS tests in a battery of standard psychophysical measures might illuminate the types of functional deficits that correlate with these apparent deficits in very rapid central processing.

The results obtained with conventional ABR methods in laboratory animals reinforce the conclusions provided by human subjects that when age effects are found on ABR amplitude and latency measures, they can most parsimoniously be attributed to peripheral hearing loss (in the old cat, Harrison and Buchwald 1982; in C57BL/6 and CBA mice, Hunter and Willott 1987; in the old gerbil, Boettcher et al. 1993; in the guinea pig, Ingham et al. 1999). As yet, there seems to be no study on the effects of MLS presentation in laboratory animals, and this represents an important gap in the comparative literature that attempts to link the effects found in humans with those of animals. But it is also important to keep in mind that both ABR methods are selective measures of fast synchronous activity in response to simple acoustic transients and that all of this neural activity is completed within just 10 ms of the onset of the stimulus. Thus although the ABR provides a very useful noninvasive measure of peripheral hearing loss and additional insights concerning brainstem processing, its scope is limited even for brainstem activity and the ABR cannot illuminate function in more rostral regions.

4.5 Central Processing Deficits: Temporal, Spectral, and Spatial Dimensions

Speech signals are complex acoustic tokens that undergo rapid spectral and amplitude modulations over time, and it is reasonable to hypothesize, as many have, that a diminished ability to track these modulations must affect speech perception. The psychophysical literature reveals that temporal acuity and frequency resolution are affected by both hearing loss and advancing age, with the effect of age increasing with stimulus complexity and background conditions. An example is gap detection, especially when combined with a spectral shift, if the task has an added fluctuating background, or when signals and noise are presented from different locations (see Fitzgibbons and Gordon-Salant, Chapter 5).

4.5.1 Neurobiological Measures of Complex Processing

The neurobiological literature concerning age effects on more complex spectrotemporal and spatial auditory processing is limited. As described previously, two single-unit studies that focused on onset neurons in the IC of young vs. old CBA mice (Walton et al. 1998) and young vs. middle-aged C57BL/6 mice (Walton et al. 2008) showed that neurons in the old CBA mouse had poorer gap thresholds and slower recovery functions than in the young mouse, whereas the cells of the middle-aged C57BL/6 mouse, with more hearing loss than the old CBA mouse, were not different in these measures of temporal acuity from those of the young C57BL/6 mouse. Finlayson (2002) measured recovery functions to pairs of tone bursts in single units of the IC of young adult and old rats with minimal hearing loss and reported that the initial suppressive effect of the first stimulus on the second was not affected by age, but the subsequent recovery functions were ~50% delayed in the old rats. A more complex method of assessing temporal resolution is to present a stimulus that does not have a single gap but consists of a series of amplitude-modulated (AM) waves that can be varied over time in their frequency or depth of modulation. Walton et al. (2002) measured single-unit activity in the IC of young and old CBA mice in response to AM stimuli and discovered that the younger cells were able to respond to faster rates. One additional finding in this experiment was that the older CBA mice had more vigorous neural responses than the young mice, this being understood as another instance of central auditory hyperactivity associated with advancing age. In a similar experiment that was focused on spectral rather that amplitude modulation, Mendelson and Ricketts (2001) measured single-unit activity in the rat auditory cortex in response to frequency-modulated (FM) sweeps that changed in speed and extent from trial to trial in young adult and old rats. Differences that could be due to audibility were minimized by eliminating any animal with ABR thresholds more than 10-dB SPL above that of the average young rat and then by presenting all stimuli at 30 dB above threshold for each of the tested single units (this being very similar to the protocol of Nabelek and Robinson 1983 that was described above). These authors reported that the majority of neurons of young rats responded best to faster rates of modulation than did the neurons in old rats, the majority of which responded best to slow rates of modulation.

There are just two published neurobiological studies of the effects of age on spatial location and on binaural unmasking, both from the same laboratory and both showing a spatial deficit in neurons of the IC in the middle-aged C57BL/6 mouse with high-frequency ARHL (McFadden and Willott 1994a, b). Specifically, they discovered a loss of directional sensitivity to best-frequency tone pips in the middle-aged mouse, a greater masking effect overall, and no benefit from providing a greater separation between the locations of the signal and the masking noise. It should be noted that mice depend on very high frequency hearing for distinguishing between sound source locations (Heffner et al. 2001), and these critical frequencies were no longer audible to the middle-aged C57BL/6 mouse.

4.5.2 AEP Studies of Complex Auditory Processing

The AEPs recorded at intervals of ~50 to 300 ms after stimulus onset are generated rostral to the brainstem, in the thalamus, in the thalamocortical pathways, and in the auditory cortex, and they are reliably evoked by stimuli having a complex time-varying spectral structure. One of the passive listening tasks is called "mismatch negativity" (MMN), which is seen in the AEP as a negative response that follows N1 ~200 to 300 ms after the presentation of a deviant stimulus (the "mis-match") that is occasionally presented in a series of otherwise identical sounds. In a study of gap detection, Bertoli et al. (2002) compared elderly humans with near-normal hearing up to 3 kHz (mean age, 72 years) with young subjects (mean age, 26 years) on an active psychophysical task and in a passive listening MMN task in which the AEPs to test tones were recorded while the subjects read a book. Most of these tones (85%) had no gap, whereas other tones (15%) contained brief quiet gaps having durations of 6 to 24 ms. In the psychophysical task, the mean gap thresholds were 7.8 ms for the elderly participants and 6.4 ms for the young participants, not quite a significant difference (the 2-tailed $p = 0.09$), whereas in the passive MMN procedure, the gap thresholds were significantly different, 15 ms for the elderly and 9 ms for the young participant. The elderly listeners with a measurable MMN had smaller amplitudes and longer latencies than the young listeners, but four elderly subjects and one young subject had no measurable MMN for any gap duration.

Gap detection depends on high-frequency spectral components of the markers for the gap in humans (Snell et al. 1994) and the large failure rate in the MMN task found in these elderly subjects suggests the possibility that elderly listeners with high-frequency hearing loss can at least partially compensate for this loss with focused attention in the psychophysical task but not in passive MMN detection.

Tremblay et al. (2003) studied the effects of age on the P1, N1, and P2 AEP responses evoked by an ordered sequence of gap durations within speech syllables, with the AEP method accompanied by a psychophysical test. These seven syllables varied in voice-onset time (VOT) between /ba/ and /pa/, the extremes having a VOT of 0 and 60 ms, respectively. Three groups were tested, young listeners (mean = 26 years), older listeners (mean = 68 years) with preserved hearing within 10 dB of the younger group, and older listeners (mean = 72 years) with high-frequency hearing loss, their thresholds being 50 dB above those of the young at 8 kHz. The psychophysical ability of the subjects to discriminate the different VOT cues was best in the young group, next in the elderly group with preserved hearing sensitivity, and poorest in the elderly listeners with hearing impairment. For the AEP measures, the latency of P1 did not differ among the groups and neither did its amplitude, but the amplitude of N1 was increased with hearing loss in the elderly hearing-impaired group, another apparent example of central hyperreactivity associated with hearing loss. Both elderly groups showed longer N1 latencies for the more delayed VOT stimuli in comparison to the young group, and P2 peaks were delayed for both elderly groups across the entire range of VOT times. These results indicate that the neural encoding of VOT is related to age alone, whereas the encoding necessary for perception is affected by both age and hearing loss. Speech perception is critically dependent on VOT, and the delayed response in older adults with mild hearing loss may explain their difficulties in understanding speech in difficult listening situations.

Another temporal cue that has been studied in older adults is the interaural phase difference (IPD), a cue that contributes to the perception of sound location. Using magnetoencephalography (a procedure that measures an auditory evoked magnetic field generated in the brain, yielding an AEF rather than an AEP), Ross et al. (2007) measured the P1-N1-P2 complex to assess the effects of aging on the physiological capacity to detect interaural timing cues Fig. 4.5. The passive recording paradigm included stimuli being presented through insert earphones that included a change in IPDs within a succession of simple stimulus onsets and offsets while the participants watched a silent movie. Three age groups were tested in this experiment, young adults (mean = 26.8 years), a middle-aged group (mean = 50.8 years), and an elderly group (mean = 71.4 years). The middle-aged mean hearing thresholds were no more than 5 to 10 dB poorer than those of the young group, whereas the old group had a relative hearing loss of ~10 to 15 dB for the low frequencies up to 1,000 Hz, rising to 50 dB at 8 kHz. The stimuli were 40-Hz AM signals. For the first 2 seconds, the stimuli were diotic, i.e., the two ears received the same stimulus in phase, then for the last 2 seconds the presentation was dichotic, with the tone in one ear 180° out of phase with the other ear. The active psychophysical task consisted of listening to pairs of 1-second-long diotic and dichotic stimuli at 1 IPD presented in semirandom order and choosing which stimulus was separated between

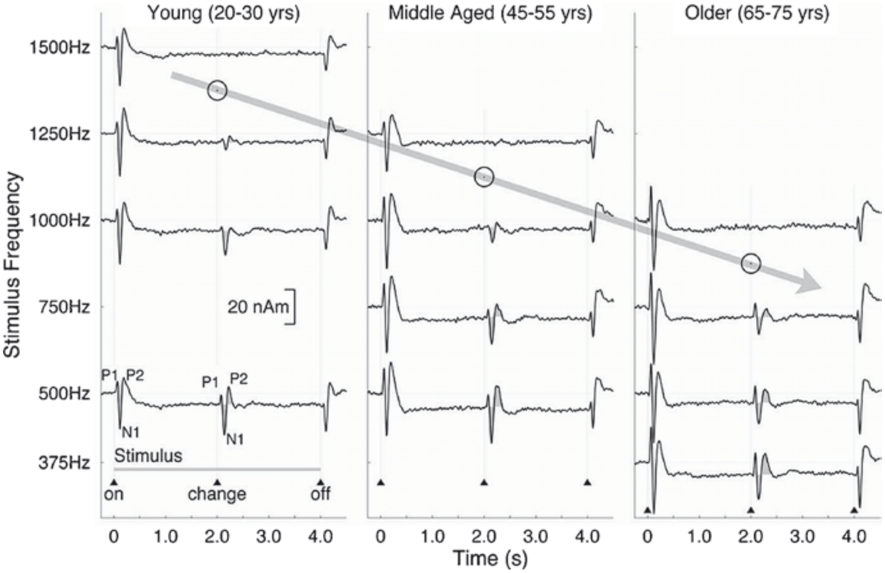

Fig. 4.5 Grand averaged auditory evoked fields (AEFs) for 3 age groups and for each test frequency. At the lowest frequency, all age groups provided an AEF to the phase shift that occurred at 2 s, but then the amplitude of the response diminished with increasing frequency and disappeared near each behavioral threshold frequency (circles connected by the arrow). (Reprinted from Ross et al. 2007, Fig. 3, with permission.)

the 2 ears (i.e., the dichotic presentation). This session began with the longest IPD and then adaptively converged on a threshold.

The AEF data are shown in Fig. 4.5. It is evident that clearly defined onset and offset responses were present and equal in all age groups and for all frequencies, suggesting that there were no age differences in the ability to detect the onset of the AM stimuli. The onset response was in fact largest in the oldest group, and this appears to be another example of hyperreactivity in elderly subjects. However, greater responsivity may also have resulted because these stimuli were presented at equal decibel SL for all groups: it is possible that (here and in some other studies) using SL as the reference level may result in a greater perceived loudness in the hearing-impaired group because of loudness recruitment. All age groups had their most prominent AEF amplitudes when the IPD was introduced for the lowest frequency. The amplitude of this response declined with an increase in tonal frequency, most rapidly in the oldest group with their threshold for responding between 750 and 1,000 Hz, more slowly in the middle-aged group, with their threshold between 1,000 and 1,250 Hz, and most slowly in the youngest group that overall was the most sensitive to these stimuli, with the group threshold between 1,250 and 1,500 Hz. In addition to these effects, old age had a much stronger impact on the latency measures for this IPD change condition, with P2 being especially delayed for the elderly group beyond the range of the younger groups.

The physiological and the median perceptual thresholds for the IPD were similar in that both measures showed a decline with increasing age, but the variability in the perceptual measure was much higher. Although two members of the middle-aged and elderly groups performed as well as the best of the young subjects, four of the middle-aged group and five of the oldest group achieved no more than a chance performance on the psychophysical test while performing well on the physiological test. The contrast between perceptual and physiological thresholds found here is the opposite of that reported by Bertoli et al. (2002) who found the more expected result that active attentive listening provides lower detection thresholds than passive listening for the elderly listener. These data suggest the possibility that some older subjects were unable to make use of the neural response that could be measured as an AEF, although it is also possible that the difference between the way in which the stimuli were presented in the AEF and the psychophysical task was responsible for the differences in performance.

Harris et al. (2008) looked at the effect of age on frequency discrimination and measured the P1-N1-P2 complex in response to a brief change in a standard continuous tone. Two groups were tested under passive listening conditions: a young group ranging from 18 to 30 years of age and an older group ranging from 65 to 80 years of age. There were two standard frequencies: 500 and 3,000 Hz. Pure-tone thresholds in the groups were nearly identical up to 3 kHz. As given by the AEP data, listeners in the younger group were able to detect smaller frequency excursions and, furthermore, the difference favoring the young group was greater for the 500-Hz standard than the 3,000-Hz standard: in the younger group, the relative threshold (i.e., $\Delta F/F$) was lower for the 500-Hz standard, whereas in the older group, the relative threshold was lower for the 3,000-Hz standard. This effect had been found previously in a psychophysical study from the same laboratory (He et al. 2007), where it had been reasonably interpreted as revealing a deficit in temporal processing in the elderly listeners who were less able to make use of changes in the small differences in the fine structure of the low-frequency standard. This interpretation is similar to that of Ross et al. (2007) for the effect of age on encoding an IPD. Similar age effects were evident as well in latency and amplitude measures, with longer latencies in the older group and also higher amplitudes at 500 Hz but lower amplitudes at 3,000 Hz.

4.5.3 Behavioral Studies of Complex Auditory Processing

Behavioral studies in old animals parallel these AEP studies in humans, including the effects of increased age on gap detection, on spatial location and spatial release from masking, and, finally, on frequency selectivity. Barsz et al. (2002) described a set of three comparable experiments concerned with gap detection that fits very well with the theme of this chapter, providing comparisons of psychophysical gap thresholds in young and old human listeners (young between 17 and 40 years of age and old between 61 and 82 years of age); behavioral gap thresholds in young and old CBA mice (young mice between 2 and 3 months compared with old mice between 24 and 25 months); and electrophysiological gap thresholds in phasic IC neurons from young CBA mice (between 2 and 4 months) and old CBA mice (between 25 and 30 months old). The details of the procedures are presented in Barsz et al. (2002): humans were tested in a standard adaptive procedure to determine thresholds, the mice were tested in a reflex modification procedure, and the mouse neurons were tested with brief gaps placed near the center of noise bursts. The mean gap thresholds for young vs. old humans were 2.6 vs. 3.7 ms; the thresholds for young vs. old mice were 2.9 vs. 4.9 ms; and the thresholds for young vs. old IC cells were 2.7 vs. 26 ms. All three of the gap threshold age comparisons were statistically significant. Absolute hearing thresholds were also significantly different between young and old subjects, both mice and humans, in each case better in the younger group. Hearing thresholds for the human listeners and response thresholds for the cells were not significantly correlated with gap thresholds, but for young and old mice combined, the correlation was significant, $r = 0.45$; i.e., the greater the hearing loss, then the higher was the gap threshold. A second regression analysis performed after the effect of absolute sensitivity was removed from the data revealed a significant effect of increased age on the gap threshold that was independent of hearing loss.

Turning from gap detection to sound localization, Heffner et al. (2001) reported that middle-aged C57BL/6 mice with high-frequency hearing loss were less able to discriminate between sounds from different locations in young mice; this is consistent with the observations of McFadden and Willott (1994a, b) that in contrast to young C57BL/6 mice, single cells in the IC of middle-aged C57BL/6 mice are less sensitive to differences in sound source along the azimuth and also show less benefit in signal detection from increasing the spatial separation between signals and maskers. In mice, sound location primarily depends on the interaural level differences that are provided only by high-frequency stimuli, and these are no longer available to the middle-aged C57BL mouse.

It is thus of interest to determine whether an old mouse with maintained high-frequency hearing would show these deficits. Ison and Agrawal (1998) examined the effect of having a signal and its masker presented from the same location or separated 180° apart in the free field as a function of signal frequency and level (4 and 25 kHz, presented at 10-dB intervals between 30 and 80 dB) and of age (4 vs. 20 months). The masker was a 1-octave narrow-band noise centered on either 4 or 25 kHz and presented at 50-dB SPL. The mice were the F_1 hybrid offspring of a CBA male and a C57BL/6 female, mice known to have less hearing loss with advancing age than even the CBA parent. Compared with the young mice, the older mice had a greater ABR hearing loss of just 5 dB at 24 kHz, ~12 dB at 4 kHz, and near 0 dB at 20 kHz. The effectiveness of the signals was measured in their inhibition of the startle reflex elicited by a noise burst. The effect of spatial separation depended on the stimulus and the masker frequency, so that the inhibitory effect of the 24-kHz stimulus was greater when this signal and its 24-kHz masker were separated in space, whereas the effect of the 4-kHz stimulus was not affected by the relative position of this stimulus from its 4-kHz masker. It is noteworthy that these effects were the same in young and old mice, indicating that in the absence of peripheral hearing loss, there was no loss of spatial localization ability. It is generally thought that this benefit of spatially separating the masker from high-frequency signals results because the subject, usually a human rather than a mouse, is able to selectively attend to the ear with the better signal-to-noise ratio, and the results of this experiment suggest that these older mice had maintained this ability. The data are similar to those provided by Gelfand et al. (1988) showing that aged human listeners with good high-frequency hearing benefit from the separation of noise from signal as much as the young do.

In contrast to the mouse, the rat has a more distinct and substantially larger medial superior olivary nucleus (Harrison and Irving 1966) and so may be expected to make better use of IPDs to locate low-frequency stimuli. Brown (1984) studied the trained performance of rats when they pressed bars to the right or left of a center orienting bar. Which bar was pressed depended on the location of a brief noise pulse from a speaker that was 1 meter to the left or right of the orienting bar. Brown used a longitudinal life-span experimental design in which he began training the rats at 3 months of age and continued testing for 5 times/week (save for school vacations) until they neared the end of their life span at 21 months of age. Their discrimination performance was stable from 10 to 14 or 15 months of age, averaging ~90% correct responses, and then steadily declined as they approached 21 months of age to an average below 70%. In contrast, performance was maintained over this time interval at 100% success in a visual discrimination task. The author noted that these rats would have little absolute threshold loss (which agrees with the more recent data of Stenqvist (2000) that were obtained in the same strain) and thus concluded that the performance decrement resulted from a decline in the ability to use binaural timing cues. He pointed out that this conclusion was consistent with the histopathology data in the auditory nerve, cochlear nucleus, and superior olivary complex observed in the rat by Feldman and his associates (see section 2.2 above) and consistent also with the results of a study of elderly human listeners by Herman et al. (1977).

May et al. (2006) provided a study of changes in the auditory processing of spectral cues in old mice that is also important because it is another of these rare longitudinal studies of “life-span” ARHL. These authors began training and testing a group of mice at ~1 month of age and then continued the experiment until the mice were close to 30 months, i.e., beyond the average life span of mice. The specific rationale was based on the possibility that age may increase the width of the spectral filter in mice as had been previously shown in human listeners by Patterson et al. (1982). This phenomenon seems particularly useful for understanding the problems of signal detection in noise (which is one of the signature complaints of the elderly listener) because a filter centered on a particular signal is also sensitive to the immediately surrounding noise, which will serve to mask the signal; thus a wider filter must allow greater masking of a central signal in the presence of broadband noise. But although auditory filters are typically conceived as a peripheral mechanism that, e.g., occupies a particular swath on the basilar membrane, filter bandwidth can also be affected by a central cholinergic-based mechanism as the previously described experiment of Pickles and Comis (1973) has shown. May et al. (2006)

measured the width of the auditory filter by looking at the degree of masking of a tone by a flat broadband noise and measured the relief from masking provided by inserting quiet notches into the noise centered on the signal. Tracking the loss of masking with the increasing width of the notch provides an estimate of the filter width, given well-established algorithms developed in the human psychophysical laboratory. Fig. 4.6 presents the data for masking and derived filter shape as a function of the gap width at 2 ages, the baseline taken when the mice were less than 12 months and the final data when the mice were over 24 months of age. For the 11.2-kHz test tone, masking increased by ~10 dB overall as a function of age, but for the 16-kHz test tone the initial 15-dB masking effect increased as the notch widened from near 0 to 50% of its center frequency. The effect seen at 11.2 kHz may be an indication that the efficiency of signal-to-noise processing has weakened in the old

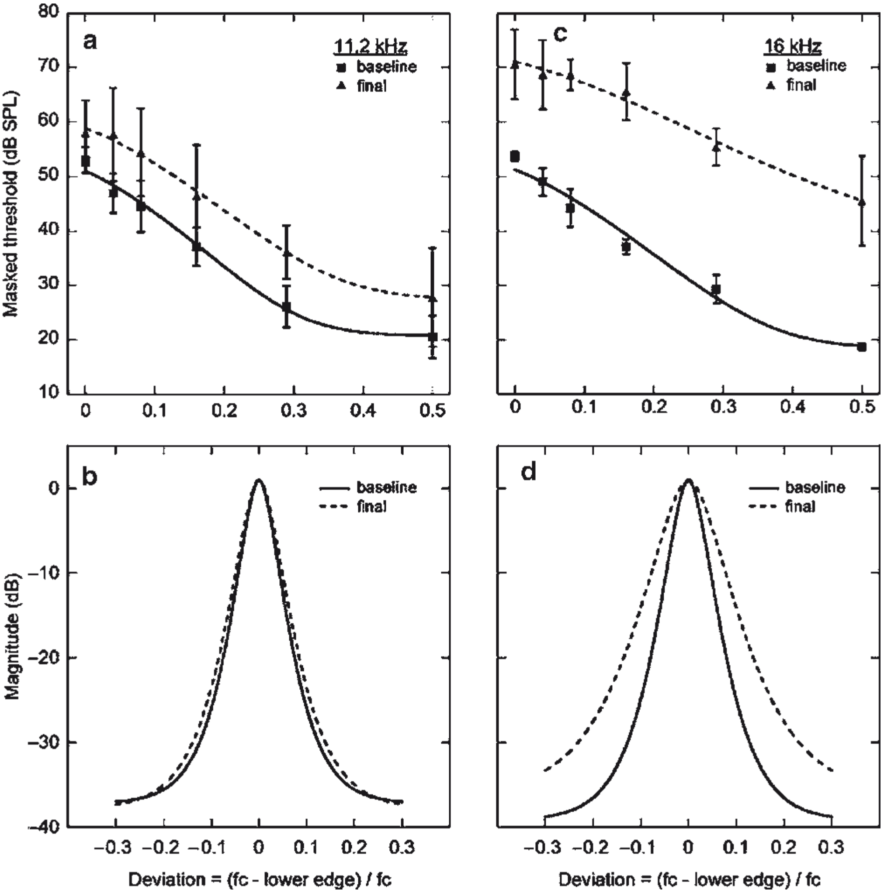

Fig. 4.6 Masked threshold in groups of mice tested when young (baseline) and near the end of their life span (final) at 11.2 (**a**) and 16 kHz (**c**). (**b** and **d**) Calculated filter shapes at these 2 ages. (Reprinted from May et al. 2006, Fig. 7, with permission.)

mouse, but the shape of the auditory filter has not (Patterson et al. 1982), whereas the effect at 16 kHz can be interpreted as showing both a loss of efficiency and a widening of the filter in the near-senescent mouse. It is of additional interest that changes in the filter shape did not correlate with the severity of absolute hearing loss, as the mouse that showed the largest degree of hearing loss at 16 kHz had a well-preserved filter shape for that frequency, whereas a mouse that had an extreme increase in filter width had only an average threshold change.

4.6 A Summary of Past Research and Its Implications for Moving Forward

Different animal species have been variously proposed as being the most appropriate animal model for human ARHL based on different criteria. Factored into these decisions may be a set of practical criteria favoring rodents with their relatively short life span that are reasonably inexpensive to acquire and maintain and that remain healthy in a vivarium setting. Another criterion is the similarity between the appearance of ARHL in the animal model and the common phenotypes obtained in human studies of ARHL, although there is some disagreement about the “true” phenotype of pure ARHL. As described in section 1.3 above, although many investigators would accept the pattern of steeply rising hearing loss for the high-frequency hearing seen in Figure 4.1A as representative of human ARHL, others point to the potential confound between chronological age and the cumulative effect of noise exposure, e.g., that may contribute to high-frequency hearing loss. This approach suggests that the less sharply rising profiles of hearing loss that were also present in the data of Allen and Eddins (2009) better represent biological aging. Other criteria reflect the similarity between the animal’s genome and that of humans, in which case primates would be preferred (Bennett et al. 1983), or their having a long life span because some effects of aging might well differ with chronological rather than biological time; this favors an animal such as the cat or the chinchilla that have life spans approaching 20 years (McFadden et al. 1997). And most recently, new criteria to be considered are the opportunity to study the genetics of ARHL in inbred and hybrid strains of mice (e.g., Erway et al. 1993) and the relative ease of manipulating the mouse genome by genetic engineering (e.g., McCullough and Tempel 2004). This is no doubt the reason why the mouse model has in the last decade become the most preferred animal model of ARHL, although economy of upkeep and a relatively short life span have always added to its attractiveness. Fortunately, the basic phenomena of human ARHL have been found in all mammalian models for both absolute thresholds and complex auditory processing and including animals that provide both sharply rising and flatter profiles of hearing loss. This is a reassuring finding because it means that animal models can be chosen freely for their best fit to the needs of hypothesis testing; thus a hypothesis about the effect of high-frequency hair cell loss on central tonotopic reorganization could be tested in the C57BL/6 mouse (Willott 1986), a hypothesis about the interaction of age and noise exposure could be tested in the CBA mouse (Kujawa and Liberman 2006), and a hypothesis concerning the effects of age on sensitivity to interaural time differences and spatial localization could use the rat (Brown 1984) or the gerbil in an extension of the research on gerbils by Heffner and Heffner (1988).

Most impressive in both the animal and the human literature is that all of the functional data show substantial variation among individuals in hearing ability within an age group, perhaps not surprising in humans because of the great diversity in genetic background and experience in our species but also present in at least a reduced form between inbred animals of the same age that have been maintained in well-regulated environments (Ison et al. 2007). This pattern of variation suggests there may be significant effects on hearing of seemingly insignificant differences in the pre- or postnatal environment and raises as well the possibility of different patterns of epigenetic gene expression even between animals with seemingly identical genes. Not surprisingly, most experimental reports in hearing science focus on the significant differences between different age groups rather than the presence of individual differences within a group, but some researchers have shown that it is possible to use these individual differences to advantage. There are exemplary attempts to address the problem of individual differences in the animal laboratory by looking for their correlates in other neurobiological indices. For example, Tarnowski et al. (1991) examined the association between threshold measures at specific frequencies and counts of regional hair cells in a large group of old gerbils with varied degrees of hearing loss. These authors concluded that overall differences in thresholds among animals were correlated with their overall hair cell loss, and careful readers of their very informative figures will note also that the gerbils that were outliers in the degree of frequency-specific hearing loss appeared also to be outliers in their site-specific hair cell loss. Ison et al. (2007) were able to correlate individual differences in age-related low-frequency hyperreflexia in the aging inbred C57BL/6 mice with their degree of high-frequency hearing loss, suggesting that the degree of peripheral hearing loss was in part responsible for their individual differences in this abnormal behavior. Hequembourg and Liberman (2001) found that degeneration of fibrocytes in the spiral ligament was associated with a small decline in the ABR and predated the loss of hair cells in the C57BL/6 mice associated with the rapid progression of hearing loss, raising the interesting hypothesis that the composition of the cochlear endolymph may have some interactive role in the genetically determined progression of hair cell loss in this mouse strain. The lesson of these examples is that unique insights can be realized in multidisciplinary research projects that have a broad range of end points, including the correlations between and within functional and neurobiological measures that may then suggest causative hypotheses to be tested. Individual differences in neurobiological measures have only infrequently been noted, but it would be of great benefit to document their extent and their co-occurrence with individual differences in functional end points, as searched for in a study of human temporal bones by Nelson and Hinojosa (2006).

The major goal of this chapter was to provide the behavioral link between auditory psychophysics in aging humans and neurobiology research in aging animals. This link has been established most strongly for the deterioration of absolute thresholds in aging animals and aging human listeners, in some measure because many of the indices of cochlear pathology seen in animals are also open to investigation in human temporal bone specimens, and there are many studies of absolute thresholds in both humans and animals. The link has been less well developed between neurobiology and age-related deficits in complex auditory processing in humans and animals because the range of neurobiological observations available in humans is as yet much less developed than it is in animal models, whereas in contrast, the range of complex tasks completed in studies with human listeners is much greater than has been available for animal models. There are well-documented neurobiological indices of both peripheral and central deterioration with advancing age in animals in neurochemistry, connectivity, synaptic counts, and gene expression, but the evidence for similar effects of aging on the central auditory system in humans is at present limited and the further development of noninvasive methods for studying these end points in both animals and in humans would be very useful.

It is also clear that certain conditions accelerate ARHL (or perhaps mimic ARHL), e.g., exposure to loud noises and ototoxic drugs and systemic pharmacological manipulations and brain-lesion effects, all of which can also be demonstrated in animal models and observed in human research participants or, sometimes, patients. But it must be acknowledged that many of the neurobiological and functional studies of aging in animals and in humans have not been sufficiently well coordinated to foster integration across disciplinary lines or across species. A full accounting of presbycusis is best approached in a multidisciplinary and comparative research program in which data for multiple functional and multiple neurobiological end points are gathered not just in the same species or strains but in the same individual subjects to more directly establish the association between neurobiology and auditory processing. The search for an explanation of individual differences in the effects of age on auditory ability must rest on the assumption that their foundation is in individual differences in the neurobiological substrate.

Further advances may profit from borrowing a research design from functional programs that accumulate data for each participant on many auditory tests to study their pattern of intercorrelations (e.g., Humes 2005). At present, the results of "neurobiological tests" are typically reported separately for different end points and different neural sites, no doubt because each test result has required a major investment in time and resources. But it seems most sensible in the long-term plan to map out, e.g., how age-related neurobiological changes in one nucleus are correlated with changes in other nuclei in that same animal and whether any individual differences in these measures are correlated with individual changes in functional measures, again in the same animal. A program of this sort would depend on there being much more interaction between researchers in different disciplines than is common at present. But it is reasonable to think that translational research programs will advance most rapidly when multiple measures are taken in the same individual subjects, both animals and humans, to directly examine the empirical association between neurobiological and functional variables. A better understanding of individual differences in ARHL will help to suggest the types of interventions that will result in a beneficial functional outcome.

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