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The Development of Animal Models for the Study of Presbycusis: Building a Behavioral Link between Perception and Physiology

Elderly listeners often complain that they cannot understand what people are saying to them, a problem that may result in part from their inability to hear critical frequencies in the speech signal and in part by a failure in auditory processing that results in speech that is heard only in a distorted and near incomprehensible form. Behaviorally based psychophysical studies in laboratory animals have shown that the sensory attenuation that accompanies aging occurs in species other than humans and have served to validate other types of animal models, most often using evoked potentials, that have provided considerable insight into the physiological bases of attenuation. These animal models now have great potential as testing platforms for potential therapies intended to maintain or recover physiological function and, thus, sensory ability. In comparison, the nature of the processing deficits that may yield perceptual distortion is less well understood even in aged humans, let alone in laboratory animals. This chapter briefly reviews the development of animal models that demonstrate age-related sensory attenuation of simple auditory signals and then describes our behavioral study of a potential source of perceptual distortion in age-related changes in temporal acuity in mice. Our findings are similar to those of our colleagues who study neural temporal acuity in the aged central auditory nervous system of mice, and similar also to the data of our colleagues who study sensory temporal acuity in aged humans. This behavioral link between neurophysiology and sensation and perception supports the hypothesis that a diminished reactivity to threshold and suprathreshold gaps in noise in particular types of cells in the human auditory midbrain is responsible for distorting the perceptual representation of speech. © 2001 Academic Press.

I. The Need for Animal Models of the Presbycusic Listener

The intent of the present work is to describe briefly the possible sensory and perceptual bases of age-related hearing loss, and the continuing search for ways of capturing these psychological attributes in animal models that may aid in the better understanding of their physiological bases and, potentially, in the development of strategies for prevention and remediation. Many aged human listeners have two complaints about their diminished hearing abilities. One is that they can no longer hear certain familiar, pleasant, and important sounds, such as the telephone or the door bell, or birds singing and children playing. This is a sensory phenomenon of diminished sensitivity. The other is that while they may certainly hear people talking and saying something, they may then find it impossible to make out what it being said. This aspect of their hearing loss that affects speech perception is a very serious matter because

it undermines human communication in a great variety of contexts, and besides presenting obvious practical problems, it may lead also to social isolation from colleagues, family, and friends (Working Group, CHABA, 1988).

A question of fundamental interest is the degree to which these two have the same cause or, instead, result from separable malfunctions in basically different types of sensory/perceptual and physiological mechanisms that will require different therapeutic strategies for their remediation. The search for animal models that capture the critical elements of these two complaints and would support an analysis of their underlying causes is a challenging task: particularly challenging is the development of models that focus on the perception of complex acoustic signals, and yet it is this pursuit that seems especially important because it is here that age-related changes in brain structure and brain function are likely to play a decisive role in producing the perceptual deficits of the aging human listener.

II. Evidence for Attenuation and Distortion as Sensory Bases of Presbycusis

Plomp (1978) has described two very general categories of hearing loss in human listeners, one that he called "class A" (for attenuation) and the other "class D" (for distortion). He argued that a class A loss may be remedied by amplification, while class D is not. Drawn in broad strokes, the recent studies of these concepts of attenuation and distortion have been allied with different experimental and theoretical approaches to the understanding of presbycusis in aged humans, each suggesting a different type of underlying sensory or perceptual deficit and having a different physiological basis and a different anatomical location.

For the first of these approaches, by far the more familiar, the fact that once normally heard signals are no longer audible is understood as being a simple reflection of the clinical observation that the sensory threshold for significant spectral frequencies of acoustic stimulation is elevated in the elderly listener. Age-related changes in the audiogram are readily detected in the clinic, and there is considerable epidemiological evidence showing that a majority of aged humans exhibit a progressive loss of sensitivity for simple tonal stimuli, an attenuation effect that begins with the high frequencies and then becomes increasingly apparent at lower and lower frequencies with advancing age (for example, Pearson *et al.*, 1995; and Fig. 43.1). The change in absolute thresholds that is seen in the clinic must certainly correlate with the loss of audibility of certain sounds in the real world. As this loss of audibility must ultimately encroach on critical speech frequencies, it is plausible to hypothesize that it is responsible for the changes in speech understanding of "more-or-less audible" speech. For example, the identifying hallmarks of speech presence might be readily heard, such as its overall amplitude envelope or its relatively low-frequency vowel structure, while the especially informative high-frequency spectral cues for consonants fall below the detection threshold; thus "speech" would be heard, but not comprehended.

The evidence for the class D loss in hearing that causes specific sorts of difficulties for complex acoustic stimuli over and above those due to the class A deficit seems persuasive to

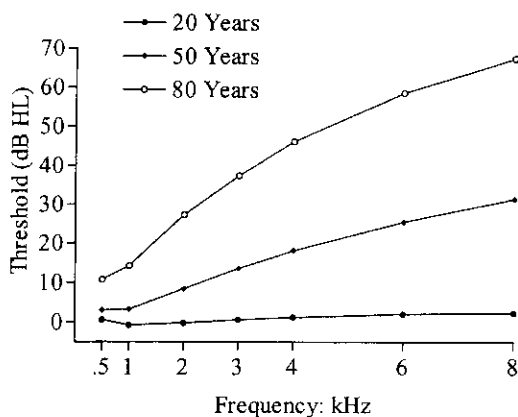


FIG. 43.1. Changes in hearing thresholds as a function of signal frequency in men of different ages. Adapted with permission from Pearson *et al.* (1995, Table III, p. 1199).

many investigators, but the supporting data are by no means as pervasive as those for the class A deficit, and there are no large-scale epidemiological studies that identify and then describe the incidence of a class D hearing loss. Then further, it is possible that the complete independence of these forms of hearing loss may be quite rare, that is, the presence of distortion may largely occur following attenuation of the auditory signal, but attenuation may not inevitably yield distortion.

Independence is perhaps best encountered as a characteristic of a neurological disorder called "word deafness," which is seen in some patients who, in contrast to patients with classic aphasia, have normal reading and writing abilities and even normal speech, but share a total inability to understand the spoken word (e.g., Buchtel and Stewart, 1989). Word deafness appears to result as a consequence of bilateral damage to the auditory cortex and thus does not provide an apt model for most presbycusis listeners. However, these case histories are important because they provide evidence of great theoretical significance in their demonstration of the complexity of the processing mechanisms that are necessary for maintaining the clarity of the speech signal. They show also, first, that speech may be uninterpretable even though its entire spectral content is perfectly audible (the audiograms of these patients are typically normal), and second, at least some of these case histories provide evidence that the deficit in speech understanding is associated with a deficit in a very simple sensory dimension, namely, temporal acuity. For this reason the tragic neurological accident that leads to word deafness has had important implications for the search for animal models of presbycusis. It is relatively easy to measure temporal acuity in laboratory animals, and though it should not yet be argued that the aged presbycusis listener has subtle neurological problems at the level of the auditory cortex, it certainly seems reasonable to hypothesize that changes in temporal acuity may be in part responsible for a class D hearing loss.

In further support of the idea that distortion and attenuation may be at least in part independent, there is a larger class of apparently neurologically intact human listeners who also have normal or near-normal audiograms, but share a very similar and isolated problem in understanding speech. They differ in one respect from the neurological patients, which is, namely, that their problem is manifest only in the presence of masking noise and not in quiet, as the word-deaf patient cannot understand speech presented in either noise or quiet. Middelweerd *et al.* (1990) studied a relatively large group of patients of this sort, who, with their mean age of just 36 years, would not be classified as being "aged listeners," but nonetheless express this particular presbycusis-like complaint. Middelweerd *et al.* (1990) found a small and inconsequential difference between this patient group and a control group of listeners both in the audiogram and in speech perception measures obtained in quiet, but reported that there were large and clinically significant differences between the two groups when speech was presented in noise. It is not known if this group of patients had a deficit in their temporal acuity or even if they would have problems in processing simple signals in noise, which is a deficit in sensory processing that could be readily investigated in the psychoacoustics laboratory; but clearly, they have problems in understanding speech in noise in the absence of any apparent deficit in their absolute thresholds.

The third source of data pointing to the importance of distortion as a distinct species of hearing loss that is set apart from changes in audibility is presented often incidentally in the reports of experiments that have attempted to characterize aged and hearing-impaired listeners as a group. Thus, for example, Glasberg and Moore (1989) report a correlation matrix for hearing impaired and mostly aged listeners (mean age 61 years) which provided measures of the relationships between speech reception thresholds in quiet and in noise with a variety of psychoacoustic measures. They showed that the correlation between an absolute threshold measure and speech reception threshold in quiet was extremely strong, essentially accounting for all of the variance in the speech thresholds ($r=0.96$). However, this correlation between the speech reception threshold and absolute thresholds was reduced in size when the speech reception threshold was obtained in noise, and in this noise condition the speech reception threshold was instead correlated with measures of acuity and resolution in the temporal and spectral domains (gap detection thresholds and frequency discrimination). Similarly, Ison *et al.* (1998) compared speech reception threshold in quiet and masking noise in a group of aged listeners with but modest hearing loss ($n=21$; mean age, 68 years) with a second group of normal young listeners ($n=19$; mean age, 22) (Fig. 43.2). The speech reception threshold measured in quiet was correlated with absolute threshold measures to the same extent in both young and old subjects, and, indeed, this difference in the class A deficit accounted for all of the apparent age difference between the groups in their speech thresholds. This consequence of the deficit in audibility occurred only in the quiet condition, and, in striking contrast, the correlations between speech reception thresholds obtained in noise and their absolute detection thresholds were close to zero. These data indicated that the age difference in speech perception in noise was not determined by their small class A deficits apparent in the audiogram and provides additional evidence for the independence of the

class D hearing loss. It is also of interest that in psychoacoustic work using a largely overlapping group of subjects, these elderly listeners also showed a deficit in temporal acuity.

There are other scattered observations indicating that the hearing abilities of aged listeners may be quite heterogeneous in their composition, and that although decrements in audibility may fully account for speech perception losses in many listeners, in other listeners decrements in temporal or spectral resolution may prove to be more important. For example, Lutman and Clark (1986) measured speech identification thresholds in noise for 23 mostly aged listeners (mean, 60 years old; range, 44–72), all having substantial hearing loss and all wearing hearing aids. Their speech measures were related to audiometric thresholds obtained at 2 kHz, but also they were related independently to gap detection and frequency resolution thresholds: these data are certainly consistent with the suggestion that changes in audibility (class A deficits) and changes in frequency and temporal acuity (which are presumably two important bases of class D deficits) make independent contributions to speech perception. However, the authors also noted that their correlation could be attributed in large part to the presence of a small group of subjects with very high gap thresholds who also required very high signal/noise ratios to correctly identify the speech signals: this observation agrees with the outcome of most aging research in its showing that the aged form a heterogeneous group of persons having diverse capabilities and, perhaps, diverse causative factors lying behind the differences of their performance from that of the young.

III. The Development of Animal Models to Study Attenuation

The reports above, and others like them, suggest that indeed changes in both the audibility and in the perceived clarity of

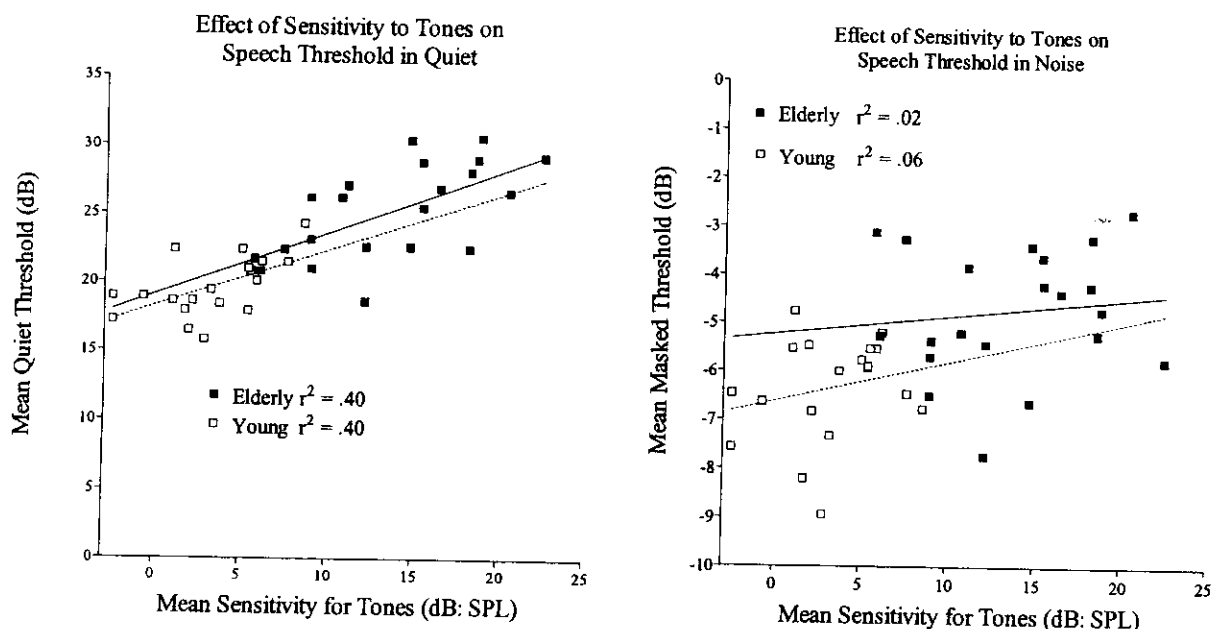


FIG. 43.2. Regression of speech reception thresholds in quiet (left) and noise (right) on the group mean audiogram, in groups differing in age (solid lines and symbols are the aged group, dotted lines and open symbols the young group). From Ison *et al.* (1998).

acoustic signals may provide two partially dissociable consequences of age that make it difficult for many aged listeners to understand speech, especially in noisy and reverberant conditions. The question then is whether it is possible to design animal models that might capture these two sensory effects in the laboratory, models that will help to understand the physiological bases of age-related hearing loss, and afford an animal testing platform for proposed therapeutic strategies prior to their clinical application.

In humans, changes in audibility are readily obtained in clinical audiograms, using a simple procedure in which the critical question asked of the listener is whether or not he or she heard the test tone. Long (1994) has persuasively argued that similar psychophysical tests based in the behavior of animals are critical to illuminating the problem of how neurophysiological events are expressed in sensation and perception. She presented the basic principles common to these tests, their difficulties in implementation, and many of their findings for the standard psychoacoustic dimensions of threshold determination, frequency processing, temporal acuity, and so forth. Comparative hearing researchers have been concerned with the limits of animal perception at least since the time of Yerkes (1905), and behavioral audiograms are available for many species of animals (see, for example, Fay, 1988). Unfortunately, there are some serious obstacles in the design and in the application of most standard psychophysical tests in animals, some of which may especially detract from their use with aged populations. This is not to say that laboratory procedures to measure sensory events in animals have not been exceedingly powerful and useful, for at best they have both of these attributes. However, many of these procedures require the use of sophisticated training procedures that are extraordinarily time intensive, and this alone severely limits the numbers of subjects that can be run in any one experiment. As a result, it is not unusual for the published and paradigmatic classical audiograms characteristic of different species to have been obtained for just two or three young animals of that species.

The results of psychophysical tests in animals are typically reliable and readily replicated in young normal animals. Thus, comparing the audiograms obtained in the hooded rat by Heffner *et al.* (1994), with those obtained in just 3 albino rats by Kelly and Masterton (1977), reveals the stability of outcomes that can be obtained in the best of these experiments. However, the restrictive use of only small numbers is a very serious impediment to aging research, especially if the degree of variability among old animals should approach that of aging human listeners. In addition, most psychophysical behavioral tests require animals who are well motivated and cooperative and are able to perform learned responses under stimulus control, and this sometimes under conditions of time pressure: aged animals in these tests may be affected by age-related deficiencies in a great variety of necessary perceptual-motor and integrative talents, and thus their performance must always be interpreted with great care.

Stimulus-controlled performance of learned behavior is undoubtedly the "gold standard" of behavioral psychophysics. Other tests have been developed that do not depend on the animal's having learned a discriminative reaction to the presence of a stimulus, often using the elicitation or the modification of simple reflex behavior. These tests are more readily applied to

large numbers of subjects and do not require the use of high-motivated and well trained cooperative subjects, but to say that they represent sensory and perceptual events in the same way that human detection experiments can be thought to represent sensory events demands some strong assumptions and, often arguments from analogy. Nevertheless, there are tradeoffs and compromises in animal testing that must be considered carefully. At best, a study of presbycusis in an animal model should not depend alone on one sort of experimental procedure, but has been embedded into an empirical and theoretical context that borrows from different research domains to achieve a coherent picture of hearing in the aging animal.

There are very few published behavioral audiograms in any aged animal that approach the level of completeness typical of the human audiogram, but one most impressive set of behavioral audiograms in the animal literature was reported by Bennett *et al.* (1983). They studied three groups of rhesus monkeys, an old group ($n=3$, 31 years of age), a middle-aged group ($n=2$, 24 years of age), and a young group (9 years of age). Thresholds for frequencies between 125 Hz and 32 kHz were assessed in an operant conditioning procedure in which the monkey learned to move its head toward the drinking tube on hearing or failing to hear a tone that normally would be presented at a particular time. The experiment required 3 years for its completion. The authors used an adaptive tracking procedure to follow detection thresholds, each examination period consisting of three 2-month-long tests given 1 year apart. The data provided by Bennett *et al.* are presented in Fig. 43.3. Like older human listeners, the middle-aged monkeys showed a loss of high frequency hearing but little change in the low frequencies compared to that seen in the youngest group. The oldest group of monkeys showed a general loss of sensitivity across the spectrum that was exaggerated for the highest frequencies, this too being consistent with the audiograms of very old human listeners. Bennett *et al.* reported also that the three oldest subjects were quite different from each other despite their long common environmental history. This is interesting: old human listeners can be very different from each other in their hearing abilities and so, apparently, are monkeys.

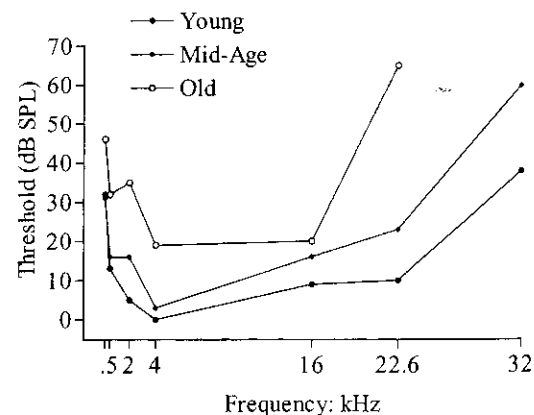


FIG. 43.3. Changes in hearing thresholds with age in monkeys, *Macaca mulatta*, as a function of age, from 9 to 31 years. Data adapted with permission from Bennett *et al.* (1983), copyright © 1983 American Psychological Association.

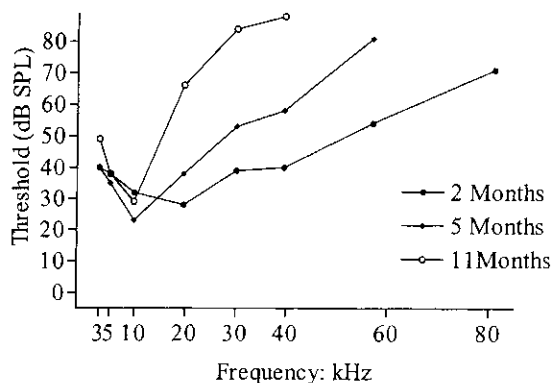


FIG. 43.4. Age related changes in threshold across frequency in three groups of aging mice. The data were adapted from Mikaelian *et al.* (1974), with permission.

Another impressive behavioral analysis of age-related changes in hearing was published for the C57/B16 mouse by Mikaelian *et al.* (1974). This was a seminal paper in its introduction of a mouse model of human presbycusis that has subsequently led to an active exploration of the genetic bases of hearing loss, its peripheral basis in the organ of Corti, and its central consequences for both structure and function. These authors trained groups of water-deprived mice to press a lever for a water reinforcement on the presentation of a tone, and then followed their thresholds for various periods of time as the mice (17 in total) aged variously from about 2 to 21 months. Figure 43.4 is a graph of data selected from their more extensive set of groups, showing thresholds at 2, 5, and 11 months. The pattern of loss is very similar to that exhibited in both humans and monkeys, in its becoming evident first at high frequencies and then progressing in its severity with age. Mikaelian *et al.* also examined the organ of Corti under the light microscope in some of these mice. They observed a loss of hair cells and supporting cells in the basal high-frequency region beginning as early as 3 months of age in this mouse, even as it entered early adulthood. This structural deterioration then progressed toward the apex and was accompanied by losses in the spiral ganglion cells, these anatomical changes roughly in concert with the loss of sensitivity.

At about the same time, Ehret (1974) published an extensive series of behavioral audiograms in a different strain of mouse that did not suffer from a relatively early onset and genetically based hearing impairment. He had developed a Pavlovian conditioning procedure in mice in which tone presentation was followed by a brief shock, so that as the mouse came to anticipate the shock it was possible to observe a facial grimace or eye blink on the presentation of the tone. Following this initial training a series of different frequencies and levels of tonal stimulation were presented in order to determine the threshold levels of stimulation that yielded responses. Ehret reported thresholds for 32 house mice ranging between 2 months and 18 months of age. The youngest mice were the most sensitive, and while subtle age differences were present variously across the tested frequency spectrum, the most systematic age-related changes were at the higher frequencies: here the performance of older mice diverged from that of younger mice at progres-

sively lower frequencies with advancing age, an outcome very similar to that described above for humans, monkeys, and the younger mouse with the early onset age-related hearing loss.

These procedures were then replicated and extended in an interesting and provocative report by Henry and Chole (1980) who used the same behavioral procedure in two strains of mice, one, the C57BL/6 related to the strain studied by Mikaelian *et al.*, which suffers from a rapid onset age-related hearing loss, and the other the CBA/J strain that, like the house mouse studied by Ehret, maintains its hearing for 18 months or more. These authors also measured auditory evoked potentials in many of the same mice, and in some of these mice they dissected out the organ of Corti in order to count the numbers of inner and outer hair cells present across the basilar membrane under the light microscope. The stimuli ranged across the spectrum between 5 and 80 kHz, and the mice ranged from 45 to 760 days in age, with sample sizes of seven or eight at the younger ages and just two or three at the oldest ages. This study thus provided a very useful comparative analysis of the correspondence between behavioral and electrophysiological functional measures and an important component of its physiological substrate, between different strains and age groups of mice.

The behavioral and the electrophysiological audiograms obtained in the youngest CBA mice were quite similar to each other, though neither showed the same sharpness of the V-shaped tuning curve that is apparent in the data of Mikaelian *et al.* The behavioral thresholds also were more variable than the electrophysiological measures, but the group means suggested a high frequency loss occurring between 200 and 470 days of age and then a large spectrumwide loss in the oldest animals. The authors noted that this audiometric pattern in the very old CBA mice resembled that of a conductive loss, and indeed, they found middle ear blockage on postmortem examination. Behavioral thresholds for the C57BL mouse were more in line with those of Mikaelian at least qualitatively, for they showed a substantial specific high frequency loss between 65 and 100 days of age, and then a complete flattening of the audiogram near the limits of the sound production equipment at 200 days and beyond. However, while electrophysiological and behavioral measures were roughly equivalent in the CBA mouse, for the C57BL mice the young electrophysiological thresholds were very much lower than their behavioral estimates, by 40 to 50 dB. Henry and Chole ascribe the poor behavioral results in the C57BL mouse to its hyperactivity and greater emotionality in the testing situation. The contrast between these behavioral results and those described by Mikaelian *et al.* reveals the importance of fitting the behavioral testing paradigm to the needs of the particular laboratory animal, with a suggestion that the Pavlovian conditioning used by Ehret and by Henry and Chole was not appropriate for the C57 strain. The appearance of discrepant observations such as this points to the need for a unifying conceptual approach to understand the apparently different outcomes of multidisciplinary paradigms.

Henry and Chole found that there were no changes in either inner or outer hair cell counts in the CBA mouse up through 470 days of age. In the C57BL mouse there were no losses in hair cell counts at 100 days of age, but a substantial loss

in thresholds of 20 to 30 dB for the higher frequencies compared to the thresholds obtained at 45 days of age. Although this might be thought of as indicating a serious disparity between structure and function in this mouse, it is now apparent that the counts of hair cells available to the methods of light microscopy are not the most sensitive measures of receptor structure, compared to the examination of stereocilia under electron microscopy. At 200 days and beyond changes in hair cell counts were more in line with changes in the audiogram.

This small list of behavioral audiograms in aged animals can be considered to be the primary justification for the belief that the sensory impact of simple sounds presented at near threshold values is diminished by age in laboratory animals just as it is in human listeners; they are also the primary justification for asserting that class A hearing losses can be modeled in the behavior of the laboratory animal. However, this short list is very far from the sum total of experimental studies of age-related changes in sensitivity in animals, but most of the studies of hearing loss in animals use not behavioral techniques but study instead some type of auditory evoked potential, often the brain-stem response.

A considerable body of research with both human listeners and animals makes it quite reasonable to argue that a physiologically based study of neural sensitivity to acoustic stimulation can serve as an able proxy for a behavioral measure of its sensory consequence. Indeed, most direct comparisons of behavioral thresholds and thresholds of auditory nerve fibers show a very strong and convincing relationship (see, for example, Pickles, 1988, p. 84). Moreover, measures of frequency-specific brain stem auditory evoked responses are routinely used in the clinic for estimating sensory thresholds in infants and difficult-to-test populations (Schwartz and Schwartz, 1991). It happens that these evoked potential estimates of sensory thresholds can be obtained as quickly and as conveniently in animals as they can in humans, which is often a welcome contrast with behavioral procedures. Further, their ready acceptance as a surrogate for psychophysically obtained audibility measures in the clinical examination of difficult-to-test humans and their overall correlation with behaviorally obtained audiograms in humans argue that they already serve audiology very well at a practical level: thus, it has seems eminently reasonable to use evoked potential measures rather than behavioral measures to study class A deficits in laboratory animals. Figure 43.5 describes brain stem auditory-evoked responses measures of threshold (the "ABR") obtained in our laboratory for C57BL/6J mice ranging from 6 weeks to 5 months of age. The qualitative appearance of these data is exactly that described by Mikaelian in his behavioral assessment of audibility thresholds in a closely related strain of mice, though in our observations the onset of severe hearing loss was much earlier than in his. Our 6-week-old and 3-month-old mice gave approximately the same thresholds as obtained by Mikaelian *et al.* at 2 months of age, but our 5-month-old mice had a much greater loss at the high frequencies. Given the similar values obtained in the younger mice this difference in the older mice seems unlikely to result from the difference in methodologies, but rather from real individual differences that might be anticipated in small groups of old mice (Li and Borg, 1991). More to the point, the overall similarity of these two sets of data attests to the validity of

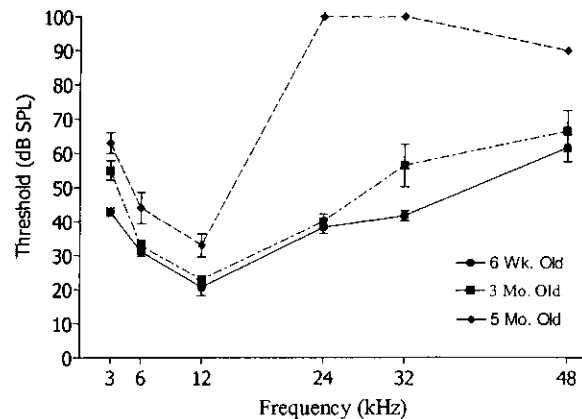


FIG. 43.5. Absolute thresholds in C57BL/6J mice obtained at three different ages, 6 weeks ($n=9$), 3 months ($n=7$), and 5 months ($n=5$). Group means \pm SEM.

the use of an electrophysiological measure of detection thresholds as a reasonable surrogate for behavioral measures of audibility.

From a practical standpoint, the electrophysiological methods have much to recommend them, for the ABR thresholds can be obtained in less than 1 h, while the behavioral thresholds may take many days, even weeks, of training and testing. As a result of this, there are many more examples of the use of evoked potentials for assessing age-related changes in detection thresholds in animals, compared to the use of behavioral thresholds. The list of aged animals that have been tested includes almost all of the laboratory animals common to auditory research, such as mice, rats, guinea pigs, chinchillas, cats, marmosets, and so forth. As a result of this large body of work, there can be little doubt that age-related loss in electrophysiologically defined threshold measures of stimulus detection is a universal phenomenon across mammalian species.

One may object that these measures of neural thresholds, most of them obtained under anesthesia, do not really assess sensory or perceptual experience. However, the general overall correspondence of the data so obtained with the data characteristic of more direct measures of sensation seems sufficient justification for their use. Besides, a philosopher with an even stricter interpretation of the nature of scientific constructs might point out that neither learned behaviors nor psychophysical judgments allow direct inspection of sensory experience in either laboratory animals or human listeners. Of course, all of the conclusions we draw from all of these experiments, regardless of their indicator response, are simply inferences about the sensory and perceptual experiences of our subjects, and their validity lies very simply in their ability to generate coherent and interesting ideas and data. Most certainly, the use of various sorts of evoked potentials in animal models of age-related hearing loss has generated an enormous understanding of the changes in the organ of Corti that underlie the decrements in sensitivity that accompany aging. Most recently these methods, together with some simple behavioral methods of reflex modification, are being used in research that is attempting to prevent early-onset age-related changes in hearing (Sundin and Willott, 1999; Willott *et al.*, 2000).

IV. An Animal Model for Studying Distortion

As described earlier, some human listeners who have normal or near normal audiograms have trouble perceiving speech, sometimes when they are in relatively quiet surroundings but particularly when people are speaking in an unfavorable acoustic environment in which competing noises and reverberation mask the speech signal: it is these data that suggest the importance of distortion in limiting the listening abilities of the aged. If it were true that the phenomenon of distortion is specific to language processing and human speech then it would of course be impossible to develop an animal model that would allow us to study its neural basis. However, the working hypothesis that the concept of "distortion" describes a set of related phenomena resulting from deficits in processing complex acoustic stimuli along perceptual dimensions other than audibility seems quite reasonable and is likely to be productive. For example, it may be that distortion results because of changes in mechanisms that aid in the processing of signals presented in noise; or spatial location, frequency analysis, or the analysis of signals that rapidly change in time; or mechanisms that maintain the integrity of a complex stimulus on the basis of the common fate of its components.

The loss of audibility of simple acoustic stimuli presented at near-threshold levels almost certainly results in large part or perhaps entirely from age-related degenerative changes in the cochlea. However, while the loss of clarity in a complex acoustic signal might result from changes in the ear, in principle it might well accompany all sorts of functional changes at any level of the nervous system where age-related degenerative processes result in the loss of neurons, perturb neuronal connectivity, or reduce transmitter release or receptor sensitivity. Not surprisingly, our understanding of the perceptual processing deficits that result in the distorted representation of acoustic events in animal models of aging and their physiological bases is much behind our understanding of attenuation. This state of affairs results in part because of a degree of uncertainty in our knowledge of the important dimensions of perceptual processing that are necessary for a faithful representation of an acoustic event even in young human listeners, as well as the difficulties in measuring such subtle effects in laboratory animals. Behavioral studies of auditory thresholds in aging animals have provided the crucial information leading to the subsequent development of the physiological bases of class A hearing loss, and it seems reasonable to suppose that comparable studies of perceptual processing deficits in aging animals will serve the same important purpose for understanding class D hearing loss.

There are several potential perceptual bases of distortion, but the following discussion focuses on temporal acuity for gaps in noise as this is the area in which our laboratories have made the most progress in collecting interdisciplinary data showing parallels between mouse behavior and both human sensory performance and animal physiology. Then further, we think that deficits in temporal acuity are likely to be present in the aged listener and are likely to have a disturbing effect of the clarity of a complex acoustic signal. There are both *a priori* and data-driven reasons for supposing that temporal acuity must be important for speech perception in the human listener. The speech signal can be thought of as a com-

plex array of sinusoidal acoustical signals that vary over time in composition and amplitude. Kewley-Port (1983) reported that certain phonemes differ only in temporal profiles of their frequency spectra on a 5-msec time scale. Our ability to identify these phonemes must depend not only on our detecting their spectral components but also on our encoding their rapidly changing temporal pattern.

Shannon *et al.* (1995) used the temporal envelope of a speech signal to modulate a wideband noise signal and then added onto this envelope an increasing number of narrow spectral bands filtered out from the speech signal. These authors reported that speech understanding was excellent even for a severely degraded signal in the spectral domain, as long as its overall dynamic pattern was maintained. Rosen (1992) has reviewed a set of these experiments that all point to the importance of the temporal cues of the speech envelope for speech understanding. These examples indicate that the ability to track rapidly changing signals must be critically important for accurate speech perception. A further interesting footnote to these ideas was provided by Turner *et al.* (1995), who showed that the ability to recognize the speech signal in amplitude modulated noise was not diminished in hearing-impaired listeners when allowances were made for their class A deficit: they argued that this supported the hypothesis that deficits in temporal acuity seen in some listeners are not limited by their peripheral hearing loss, but results from independent changes in central auditory processing mechanisms.

One of the most dramatic examples of the importance of central processing for the temporal analysis of acoustic signals is presented in the description by Buchtel and Stewart (1989) of the diminished psychoacoustic abilities of their patient with word deafness who was introduced briefly above. In addition to his near total inability to understand the spoken language, this patient suffered a major deficit in his ability to distinguish between the presentation of one versus two tone pips. He required not the usual interval between the pips of about 15 msec to make the correct discrimination, but, remarkably, he required the pips to be separated by about 300 msec. That this was an auditory rather than a cognitive deficit was shown by his normal ability to discriminate between one and two light flashes at various separations.

Some further suggestive evidence for the hypothesis that deficits in temporal acuity are the basis of the problems in speech perception seen in some aged listeners is provided in a classic report by Tyler *et al.* (1982). These authors showed that in a group of listeners differing in age and in degree of hearing loss, temporal processing as assessed by gap detection was strongly correlated with a measure of speech perception in noise. This correlation was primarily due to differences in gap detection in an older subgroup of subjects, older than the median of 58 years of age: in this subgroup the percentage of the variance accounted for by differences in gap detection approached 70%.

There are many experimental reports showing that temporal acuity as measured by gap detection thresholds does decline with age and also with high frequency hearing (for example, Buus and Florentine, 1985). Other data have shown that high frequency components of a wideband carrier make significant contributions to gap detection in human listeners (for example, Buus and Florentine, 1985; Snell *et al.*, 1994) and in mice

(Allen *et al.*, 2000): thus it might be anticipated that age-related attenuation of the high-frequency components of a gap carrier would result in a decrease in gap sensitivity. The question is, then, whether age by itself might have an independent effect on temporal acuity. Here a report by Snell (1997) is important in its showing longer gap thresholds in elderly listeners compared to those of younger listeners, even though the aged listeners were a select group with near normal hearing. The mean differences between the groups were not large, on the order of 1 to 2 msec across the various conditions, but about one-third of the elderly subjects were outside of the range of the younger subjects, and several elderly listeners had particularly poor temporal acuity. In interpreting these results, it is important to note that the correlations between temporal acuity and measures of high frequency hearing were negligible and accounted essentially for none of the variance in temporal acuity. Of course, this does not mean that in general high frequency hearing ability would not correlate with temporal acuity among a group of listeners who differed considerably in their degree of hearing impairment, but it does mean that in these groups in which aged differences were considerable (26 versus 70 years of age) and differences in thresholds were minimal, the effect of age on temporal acuity was indeed independent of changes in audibility.

Our behavioral data on gap detection obtained in mice are reasonably comparable to those obtained by Snell in the values obtained for thresholds in the mouse compared to the human listener, and in the mean differences in threshold between young and old mice. We are studying gap detection in the CBA mouse, the same mouse strain used by Henry and Chole (1980) as a model of hearing loss that occurs very late in its life span, beyond about 18 months of age. The behavioral method that we use is called "reflex modification audiometry" (Young and Fechter, 1983). The method has been used to measure sensory processing in a variety of species (see Ison and Hoffman, 1983; Hoffman and Ison, 1991), including humans. In its present application, the mouse sits in a small cage mounted on top of an accelerometer, and occasionally hears a brief noise burst that produces a flinch-like startle reaction, which is detected by the accelerometer. It is possible to use this startle reflex itself as a measure of suprathreshold hearing (Parham and Willott, 1988, for example), but for reflex modification the basic observations of interest are provided by presenting small threshold and near-threshold stimuli just prior to the startle stimulus. When presented at lead times of about 100 msec, the weak prestimulus inhibits the reflex response to the louder stimulus, and the presence of inhibition is used as objective evidence for prestimulus detection. Similar work with humans (Ison and Pinckney, 1983) has shown that gap thresholds obtained with this procedure approximate those obtained by conventional psychophysical methods. Besides its sensitivity to near-threshold stimulus levels, the great advantage of this methodology is that it does not require that the animal be trained at the task. It has also been shown that reflex inhibition for suprathreshold noise pulses presented in quiet does not vary as a function of age in mice, indicating that the inhibitory mechanisms themselves do not appear to change with age, even though reflex expression to the startle eliciting stimulus is considerably reduced in old mice (Ison *et al.*, 1997).

Over 200 mice were run in our experiment on gap thresholds in mice of different ages (reported in Barsz *et al.*, 2000), 109 below 1 year of age (range of 2 to 8 months); 42 over 1 year but less than 2 years (range 13 to 20 months); and 67 over the age of 2 years (age 24 to 29 months). The fact that many animals can be tested quite efficiently in little time is one of the great advantages of the method, compared to those methods that require the use of training, but the thresholds we obtain are about the same as those obtained with these other methods (Wagner *et al.*, 2000). It is also important that the method can be used to indicate the salience of suprathreshold stimuli, which we now believe may be more important than the simple assessment of threshold values for aging research.

The prestimulus was a gap that ranged in duration from 0 to 15 msec, that was presented 60 msec before the startle eliciting stimulus. Fig. 43.6 shows the type of data characteristic of experiments of this sort. The size of the response in each gap condition was "normalized" with respect to the baseline size of the uninhibited control condition which had no gap presented. It can be seen in all age groups that as the gap duration increased the relative size of the startle reflex diminished, rapidly when the gap increased over the range of 2 to 6 msec and more slowly afterward. The majority of mice showed an abrupt inhibitory effect for gaps between 2 and 4 msec in duration, with stragglers accounting for most of the drop in the response at the longer intervals.

It is very clear in these data that the asymptotic inhibitory effect of the gaps declined with age, this indicating that the longer gaps were less salient in the older mice. The individual data of each mouse were further analyzed in order to determine a gap threshold, this defined as the smallest gap duration that provided at least one-half of the asymptotic level of inhibition, thus providing threshold values that were independent of the asymptotic peak of inhibition. Fig. 43.7 shows the mean gap thresholds for these mice when again ranked in 1-year categories, the youngest group showing the smallest thresholds and the older group showing the largest thresholds.

These age effects for both asymptotic relative response values and for the mean gap thresholds were highly significant in the analysis of variance. These mean differences between

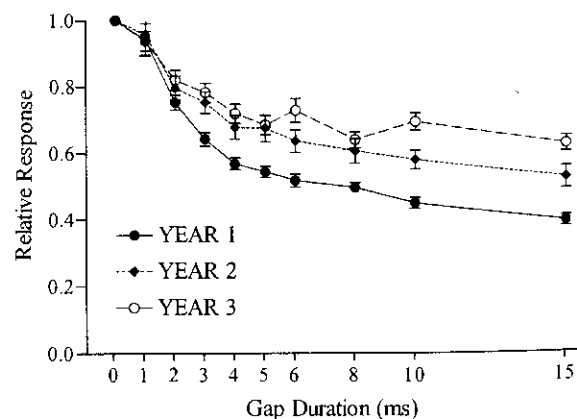


FIG. 43.6. Amplitude of the startle response (relative to the baseline control value) as a function of gap duration, in mice less than 1 year old ($n = 109$), between 1 and 2 years of age ($n = 67$), and more than 2 years old ($n = 67$).

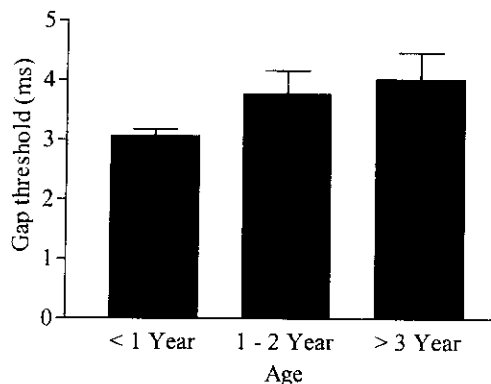


FIG. 43.7. Mean gap thresholds in mice of different ages.

the three groups in their threshold values are not extraordinarily large, but in fact they are about equivalent to the mean differences obtained in young versus old human listeners, as was shown in the data of Karen Snell. Then further, the variance in the scores within the oldest group of mice was significantly larger than that obtained in the youngest mice, and although many of the oldest mice had normal thresholds of 2 and 3 msec, about 10% had thresholds beyond the range of the younger mice.

How might these effects be explained? Our mouse experiment was different in design from that of Snell's human experiment because the mice were not preselected for their having particularly good absolute thresholds. Thus, like an unselected group of human listeners, it might be expected that, for the aged groups as a whole, measures of absolute sensitivity would be reduced in comparison to young mice. In fact, this was the case. We were able to measure thresholds in about one-third of these mice using the ABR, 37 of the youngest group, 17 of the middle-aged group, and 14 of the oldest group. These threshold data are given in Fig. 43.8. There were significant differences in sensitivity with age, with the groups being somewhat different throughout the spectrum, but different especially beyond about 20 to 24 kHz. At these higher levels, and depending on the frequency, the youngest mice had thresholds about 5 to 10 dB below those of the middle-aged group and 10 to 20 dB below those of the oldest group of mice.

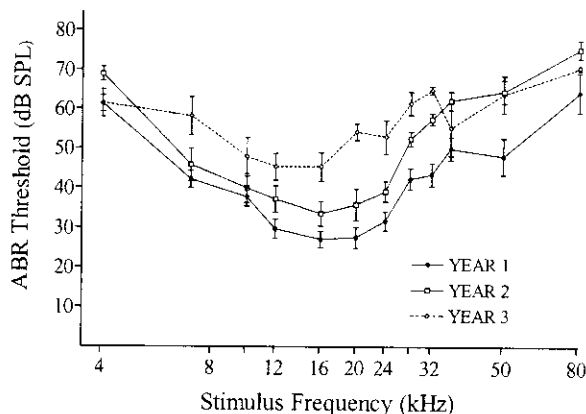


FIG. 43.8. Mean ABR thresholds (\pm SEM) in CBA mice of difference ages, within the first year (mean, 5 months), second year (mean, 16 months), or third year (mean, 25 months) of life.

Although there was no correlation between age in months and ABR thresholds within the first year of life (the range was just 3 to 8 months) there were substantial individual differences in threshold sensitivity, with the interquartile range within this group being about 20 dB. The presence of these individual differences in sensitivity to simple tone pips as given in the ABR data made it possible to determine whether differences in gap threshold would be affected by a class A hearing loss in mice. A correlation analysis of these data showed that sensitivity to moderately high frequency stimuli (the average of the thresholds taken from 28 to 50 kHz) was significantly correlated with gap detection thresholds, with the differences in threshold accounting for about 20% of variance in gap levels ($r = +0.46$). This correlation could perhaps have been anticipated because in other work we have found that in mice, as in humans, gap detection is better if the carrier for the gap has these high frequency components (Allen *et al.*, 2000), but it is an interesting confirmation of human data. It might then also be anticipated that the older mice would be less sensitive to the gaps simply because of their relatively poor sensitivity to high frequency stimuli. Indeed this may have contributed to an overall effect of age on gap detection, but in fact, we were not able to find a significant correlation between gap detection thresholds and ABR thresholds. However, we did find that in the two older groups of mice small gap thresholds could be found both in mice with poor threshold sensitivity for high frequency stimulation and in mice with good sensitivity to high frequency stimuli, but very large gap thresholds were found only in older mice that showed poor sensitivity to high frequencies in the ABR measures. The data suggest that a class A deficit may have been necessary but not sufficient to produce a deficit in gap detection thresholds.

In contrast to the small effect of age on gap detection thresholds, shown in Fig. 43.7, there was a relatively large effect of age on the asymptotic levels of inhibition, as can be seen in Fig. 43.6. A correlation analysis showed that differences in sensitivity to relatively high frequency stimuli was also correlated with the relative size of the response at the longest gap durations, the least sensitive mice showing also the least inhibitory effect of gaps at these suprathreshold gap durations ($r = 0.37$, $P < 0.01$). However, in addition, there was an equally strong effect of age alone on the level of asymptotic inhibition, there being a significant correlation between age at the time of the behavioral test and the residual inhibition values after regressing inhibition on sensitivity ($r = 0.38$, $P < 0.01$).

How might increased age contribute to a decline in the salience of suprathreshold gaps, beyond its effect on measures of sensitivity to high frequency stimuli? We believe the answer to this lies in the central nervous system, because this behavioral effect has a parallel in the neurophysiological data for suprathreshold gap durations obtained in Joe Walton's laboratory. In the young mouse both the behavioral gap threshold and the overall time course of the growth of reflex inhibition with an increase in gap duration are very similar to the neural threshold and neural responsiveness in phasic neurons in the inferior colliculus (Walton *et al.*, 1997). A later study of these types of cells in both young and old CBA mice (reported in Walton *et al.*, 1998) found two neural effects that resemble the behavioral effects shown here in Figs. 43.6 and 43.7. The first finding

was that the mean thresholds for the phasic cells were slightly elevated in the older mice, overall by about 1 to 3 msec depending on the type of cell. Many neurons in the old mouse had the same very sharp sensitivity as those of the young mouse, but there were proportionately fewer such cells in old compared to young mice. The second finding was that the recovery function to noise onset at the end of the gap was substantially prolonged in the older mice, with most young cells having fully recovered for gap durations between 5 and 10 msec in duration, whereas most cells in the older mice were not fully recovered even at gap durations of 20 to 30 msec. These age-related differences in neural responsivity to the end of a suprathreshold gap were obviously substantial, and, in contrast to the effects of age on gap thresholds, there was very little overlap between the young and the old neurons on this measure.

Thus in both sets of data, behavioral and neurophysiological, the major effects of age were seen in the diminished response to suprathreshold gaps, rather than in the gap detection threshold. This parallel outcome supports the thesis that the neural substrate for behavioral gap detection is in these phasic cells of the inferior colliculus and that the most apparent effect of age is to diminish the salience of suprathreshold events.

Our behavioral data point to two discrete and separable effects of age that diminish the perceptual significance of brief gaps in noise in the mouse, just as others have shown that two effects of age may be responsible for the changes in gap detection in human listeners. One effect is attenuation, which reduces the audibility of the high-frequency components of the carrier for the gap. In the conceptual scheme provided by Plomp, this is clearly a class A hearing loss. The other is manifest in the mouse both at the level of the neural processing in the central auditory neural system and in its behavior, and may be thought of most easily as a diminished neural responsivity to gaps which at a sensory level is represented by diminished salience, and in behavior as reduced inhibition. The ability to detect gaps has been shown to be strongly correlated to differences in speech perception among aged listeners, and the temporal attributes of the spoken language have been shown to contain an abundance of discriminative cues essential to its understanding. Thus we suspect that a diminished sensitivity to the dynamic acoustic structure of speech must result in a type of presbycusis hearing loss that may reasonably be thought of as distortion.

V. Conclusions and Thoughts for the Future

We think that in these data we have shown the importance of studying both threshold and suprathreshold effects in aged animals, and have found evidence for both class A and class D hearing loss in the acoustically guided behavior of old animals. Old mice, like old human listeners, show diminished threshold sensitivity to gaps, and, perhaps more important, show a diminished responsiveness to gaps presented at suprathreshold values. Evidence for the partial independence of class A and class D deficits in our data seems particularly interesting from the standpoint of trying to understand where class D deficits might arise. It has seemed reasonable to attribute class A deficits to deficits at the level of the organ of Corti and class D deficits to deficits in brain function. This distinction is not

completely well founded, for it has been shown that changes in sensitivity for particular frequencies might have effects other than simple attenuation at those frequencies. Thus, at the level of the auditory nerve Woolf *et al.* (1981) found that the loss of outer hair cells reduced the threshold sensitivity of high frequency fibers to high frequency stimulation but also reduced their ability to phase lock to lower frequency stimuli presented at above-threshold values. Given the importance of phase locking to certain forms of temporal processing (in particular, sound localization) it may be expected that in this case the class A hearing loss would be accompanied by a supra-threshold class D loss. In line with this reasoning, in the present experiment the class A loss was clearly correlated with a diminished suprathreshold inhibitory effect of gaps and so may be presumed to contribute to the class D hearing loss: but the separate correlation of age with inhibition is evidence that there is an additional class D loss independent of changes at the periphery.

The strong correspondence between the behavioral data and the findings from electrophysiology provided in Walton's laboratory provides a persuasive argument for the basis of this class D loss in the reduced neural response of the aged inferior colliculus at the end of the suprathreshold gap. Together these data suggest that the amelioration of the two problems of presbycusis must have two goals, one to solve the problems of the periphery, the other to solve the problems of the aged central auditory nervous system. We can imagine that this might involve neuropharmacological treatment that would boost the function of the aged neuron, perhaps by enhancing its reactivity to important acoustic events, such as gaps in noise. Then further, given recent demonstrations of neuroplasticity within the auditory system that results from exposure to certain stimulus conditions, such as the augmented acoustic environment studied by Willott *et al.* (2000), it may be possible to find other means for enriching the auditory environment in a way that will maintain auditory function with age.

The focus in the present chapter is on the contributions that an animal model of age-related changes in temporal processing might make to our understanding of presbycusis in human listeners. Obviously the distortion of complex acoustic signals may result from other sorts of deficits, such as changes in the abilities to extract signals from noise, locate sound objects in space, attend to particular signals and properly ignore others, or maintain the coherence of a complex sound object by synchronizing the processing of its component elements, for example. It seems likely that these problems too will have their bases in a combination of both peripheral and central neural mechanisms. The search for their neural bases must certainly profit from the continued development of animal models that provide the link between the physiological and the sensory-perceptual bases of behavior and offer a laboratory method for studying therapeutic effectiveness.

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FUNCTIONAL NEUROBIOLOGY OF AGING

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