

Handbook of **Mouse** **Auditory** **Research**

From Behavior
to Molecular Biology

Edited by

James F. Willott, Ph.D.

University of South Florida

Tampa, Florida

and

The Jackson Laboratory

Bar Harbor, Maine



CRC Press

Boca Raton London New York Washington, D.C.

UNIVERSITY OF ROCHESTER

25 Focus: Elicitation and Inhibition of the Startle Reflex by Acoustic Transients: Studies of Age-Related Changes in Temporal Processing

*James R. Ison, Joseph P. Walton, Robert D. Frisina,
and William E. O'Neill*

There is a growing literature on the anatomical changes in the central auditory system that accompany the aging process in the CBA/CaJ mouse, which, as described in Chapter 24, helps us understand in some measure age-related changes in auditory function, particularly the important changes in temporal acuity seen in the physiological studies that they summarize. Here we examine temporal processing in the behavioral correlates of aging, referring back where possible to certain of these anatomical and physiological effects. The subjects are CBA/CaJ mice, and also F1 hybrid mice from a C57BL/6J x CBA/CaJ cross. Both strains retain their threshold sensitivity across the spectrum until well into their second year of life, and thus provide a picture of the relatively pure effects of age on behaviors that depend on auditory processing. The history and rationale for the reflex methods used in these experiments and the procedures common to this work are given in Chapter 5. All experiments measured the acoustic startle response (ASR), as elicited by relatively intense stimuli and modified by relatively weak preliminary stimuli. This chapter addresses the question of how age affects behaviors that depend on the ability to resolve brief perturbations in the acoustic environment.

Figure 25.1 provides fundamental data on the effects of age on ASR amplitude over a wide age span, 6 weeks to 29 months, in CBA and F1 hybrid mice. The ASR was elicited by 115 dB SPL wide-band noise, 20-ms duration, ~0 ms rise and decay times, presented against a 70-dB noise background. The data come from different experiments, but all include this same baseline condition. The shape of the ASR amplitude by age function for both strains consists of an early increase in ASR vigor that reaches a peak between 3 and 6 months of age, followed then by a gradual but continuous decline. A similar decrement in the ASR with age has been seen in both rats (Krauter et al., 1981) and in humans (Ford et al., 1995). Our data agree with those provided by Krauter et al. in showing that the effect of age on this form of auditory behavior begins in middle age. The early increase in the ASR can be understood at least in part as a reflection of an increasing muscle strength in young mice up to 4 to 6 months old. The later decrement has a parallel with the changes in connectivity of the cochlear nucleus (CN) with higher centers summarized in Chapter 24, which also first appear in middle age. It may, however, have multiple causes located at both central and peripheral sites. Thus, for example, skeletal muscle changes with age to include a greater ratio of slow twitch fibers (Einsiedel and Luff, 1992), compared to the fast twitch fibers important in the fast and vigorous ASR. It is also possible that neural transmission from sensory to motor control

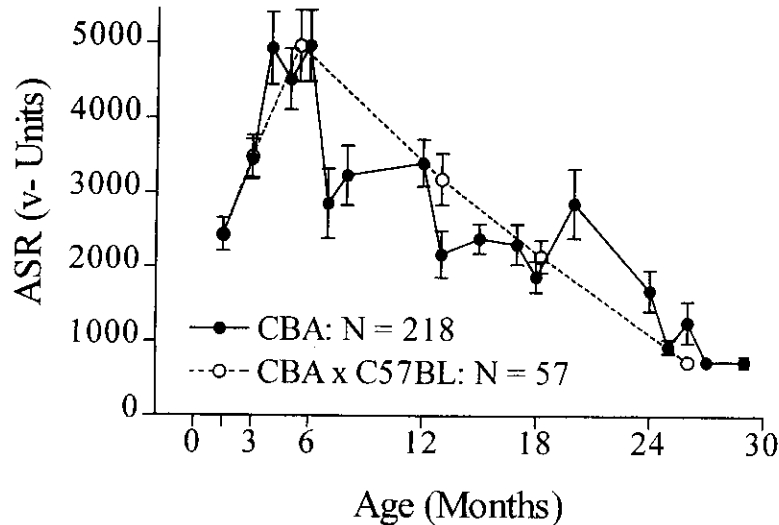


FIGURE 25.1 Mean amplitude of the ASR (\pm SEM) as a function of age in CBA mice and in the F1 hybrid offspring of a CBA/CaJ sire and a C57BL/6J dam. The startle stimulus was a 115 dB SPL noise burst (20 ms in duration) and a 70 dB noise was always present. The ABR is measured as the integrated output (100 ms) of an accelerometer under the floor of a test cage. See, for example, Ison et al. 1998 for procedural details. Note the increase in ASR amplitude in both strains up to about 4 to 6 months of age, and then the terminal linear decline.

neurons may be less effective in aging mice, and certainly age affects the integrity of the octopus cells of the posterior ventral CN (Willott and Bross, 1990). Their role in the ASR is not certain, but they have desirable structural and physiological characteristics that would usefully contribute to its rapidity and its vigor. Three major variables that affect the ASR are the level and the duration of the eliciting stimulus and the presence of background noise. Hogan and Ison (2000) examined these variables in hybrid mice aged 3, 12, and 30 months, with stimuli of 1, 2, 4, 8, and 16 ms in duration, and levels of 105, 115, and 125 dB SPL. These stimuli were presented in quiet and in 70-dB wide-band noise. Figure 25.2 suggests that the age-related changes shown in Figure 25.1 depend in detail on both the level of the startle stimulus chosen in those experiments and on the presence of background noise. Young and middle-age mice show the usual substantial facilitation of the ASR by noise, especially at the higher stimulus levels (note especially the 3 to 1 increase in 12-month-old mice, which required a change in the scale along the y-axis, and the increase of about 2 to 1 in 3-month-old mice). In contrast, the ASR for the oldest mice was depressed by noise at the lower levels and shorter durations of startle stimulus input, and was not enhanced by noise at the highest stimulus level. Evidently, noise loses its normal positive "arousal" effect in old mice, and also more seriously suppresses the ASR to weak startle inputs. This is an intriguing finding, but the major rationale for the experiment had been to examine age effects on temporal integration. In this regard, while some age differences in ASR growth rate with increased duration can be seen in the data, they primarily occur at lower stimulus values and seem to mostly relate to increases in noise-produced masking and to changes in ASR thresholds with age. The fact that the overall shapes of the functions obtained with 125-dB stimuli are very similar at the three ages suggests that there is no intrinsic age-related change in temporal integration for the ASR.

Turning now to reflex modification, the offset of a noise just prior to the onset of the startle stimulus has a substantial inhibitory effect on the ASR: how might this effect vary with age? Ison et al. (1998) examined the effects of noise decrements of 10 to 40 dB in a 70-dB background on the relative ASR to 115-dB startle stimuli in CBA/CaJ mice (Figure 25.3). Overall the effect of the decrement was greater with larger decrements up to asymptotic values of about 30 to 40 dB, and

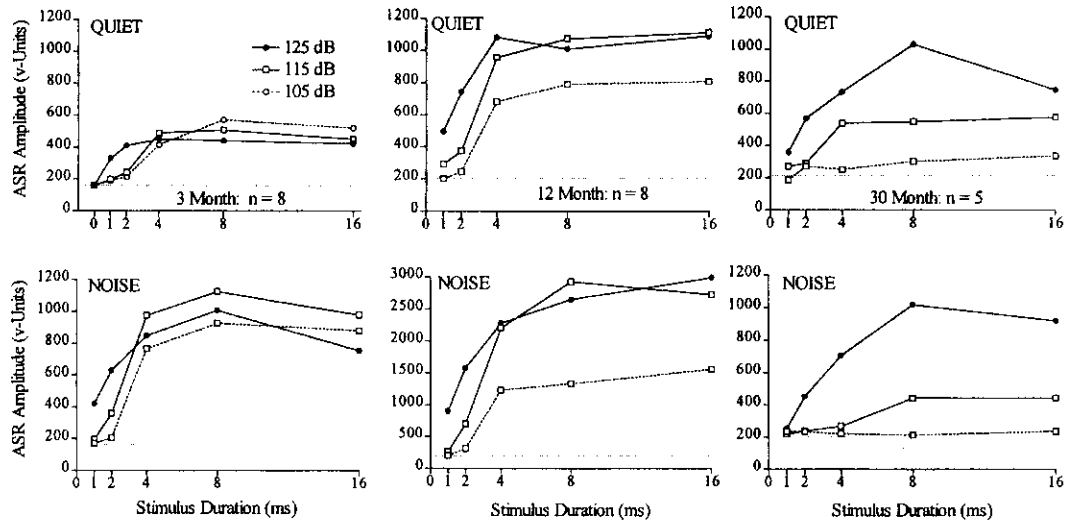


FIGURE 25.2 Mean amplitude of the ASR as a function of age in F1 hybrid mice when the eliciting noise burst stimuli were varied in duration (1, 2, 4, 8, and 16 ms) and level (105, 115, and 125 dB SPL), and these stimuli were presented in quiet (in the upper graphs) or in noise (in the lower graphs). Note the increase in the ASR with background noise in young and middle-aged mice, but not old mice; and note that in quiet, the age effects in the ASR are relatively small, especially with the higher startle level. It is hypothesized that the longer high-intensity startle stimuli evoke a self-limiting recurrent inhibitory process in younger mice. The dotted lines provide a “no-stimulus” activity level.

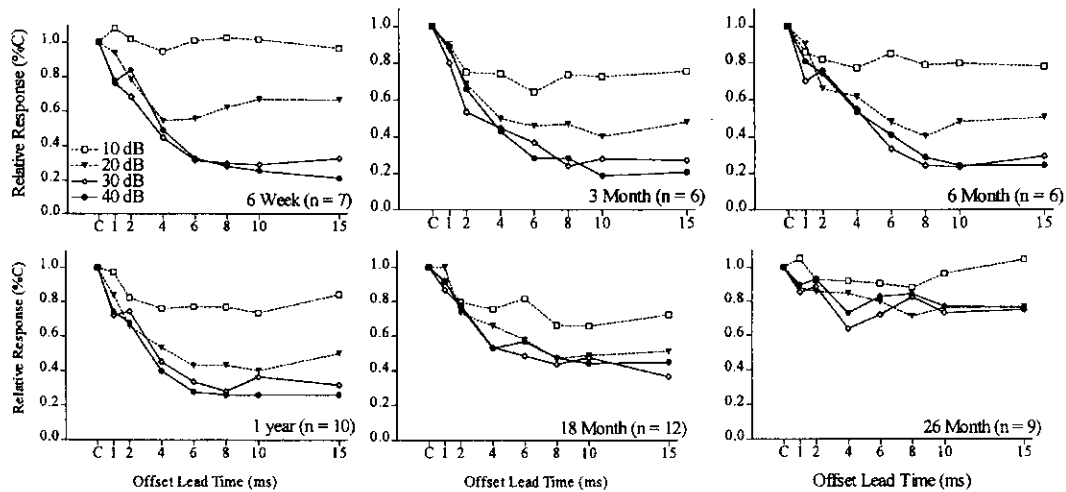


FIGURE 25.3 Mean relative ASR amplitude (percent of control responding) when the startle stimulus was preceded at different lead times by a decrement (of 10, 20, 30, or 40 dB) in a 70 dB noise background, as a function of age in CBA mice. Note especially that ASR inhibition is stronger the greater the decrement in the noise background, develops very rapidly, and reaches an asymptote between about 6 and 10 ms across conditions. The major age effect age is reduced asymptotic inhibition.

also with an increase in its lead time up to asymptotes reached at about 6 to 10 ms. Time constants generally were lower for the smaller decrements, and the youngest mice showed no inhibition for the decrement of 10 dB, suggesting a relative insensitivity to small decrements. However, there was otherwise little sign of age-related effects on the shapes of the four functions in the first year

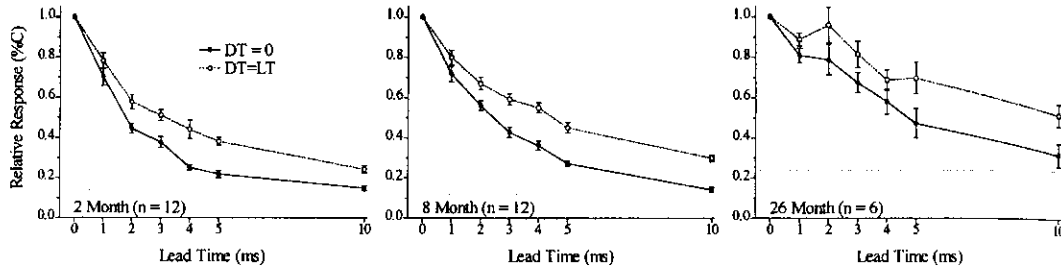


FIGURE 25.4 Mean relative ASR amplitude (\pm SEM) when the startle stimulus was preceded by noise offset at different lead times (LT) in hybrid mice as a function of age. Noise offset was either abrupt (Decay Time = 0) or had a decay time that equaled the lead time (DT = LT). Inhibition developed very rapidly, and the difference between abrupt offset and the more gradual offset was apparent for a 1-ms decay time, regardless of age. Old age was associated with reduced asymptotic inhibition.

of life. At 18 months, the mice remained sensitive to the 10-ms decrement, but decrements of 30 and 40 dB were less effective in producing inhibition. This tendency was then exaggerated in very old mice, which showed reliable but reduced inhibition for the larger decrements. There were clear and significant differences in asymptotic levels of inhibition beyond the age of 12 months, but no indication of any age-related change in the time constant for ASR inhibition with increasing lead time. The overall effect is similar to that of Figure 25.2, where there is no age effect on the time course of integration of excitatory input on ASR elicitation but the asymptotic ASR is reduced. These data sets both show that transient stimuli generally lose their effectiveness with age. In addition, we can conclude that the decline in ASR inhibition must be greater than that for excitation because inhibition is measured against the weakened excitatory impulse produced by eliciting stimuli: if age effects were equal for both inhibitory and excitatory processes, then relative inhibition would be stable across age.

Because the inhibitory effects of noise offset on the ASR are evident with lead times of just 1 ms, it seems certain that the neural processing for this form of inhibition must involve a minimal number of stages that are probably confined to the CN. While onset cells of the CN are constructed and sited so as to integrate across frequency, their special membrane characteristics minimize temporal integration for continued excitatory input (Golding et al., 1999) and thus the fact that the time constants for the growth of excitation do not vary with age should not be surprising. However, the stability of time constants for inhibition seems more remarkable, and one particularly compelling example of stability in temporal processing across age is given in the next set of data (see Figure 25.4, taken from Ison et al., 1999). Here, hybrid mice at three ages (2, 8, and 26 months) were presented with noise offsets under two conditions: one in which offset decay time was abrupt (DT = 0), and the other in which the decay time equaled the lead time (LT) by which the beginning of the offset preceded the startle stimulus. Quite obviously, ASR inhibition increased with offset lead time and was greater for DT = 0 than DT = LT; and further, younger mice showed more inhibition. However, a more subtle finding emerges from these data. The procedure was taken from von Bekesy (1960/1930) and Miller (1948) to track the hypothetical decay of sensation at noise offset in young mice, and to determine if this function changed with age. Their idea was that if the sensory effect of abrupt decay is equal to that of a non-zero decay time, then the internal decay of excitation for that abrupt offset can be no faster than the objective non-zero decay time. Conversely, if the abrupt decay yields a bigger sensory effect, then the internal rate of decay must be faster than the objective non-zero decay rate. Two important features of Figure 25.4: (1) abrupt offsets with a 1-ms lead time were more inhibitory than the equivalent 1-ms decay time, indicating that the internal rate of decay was very fast; and (2) this difference did not vary with age. This very sophisticated measure of one form of temporal acuity showed absolutely no trace of an age

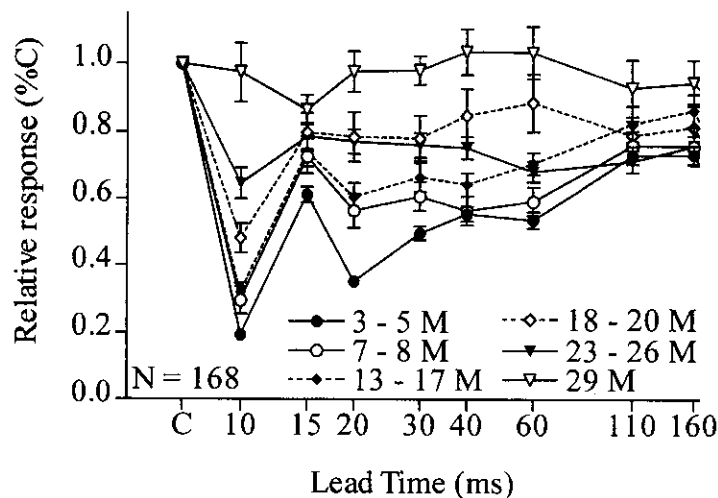


FIGURE 25.5 Mean relative ASR amplitude (\pm SEM) when the startle stimulus was preceded by a 10-ms gap in a background noise, the gap beginning 10 ms to 160 ms prior to startle onset, as a function of age in CBA/CaJ mice. In young mice, two phases of inhibition occur in rapid succession, just 10 ms apart. With increased age, the overall levels of inhibition are reduced and the second phase of inhibition is delayed.

effect; thus, in all of the data described thus far, age seems to diminish the asymptotic excitatory and inhibitory effects of transient stimuli without affecting their intrinsic rate of growth.

All of the behaviors described to this point can be attributed to neural processing at early brainstem levels; and it might be expected that as this information ascends to more rostral sites, the effects of the reduced output of the caudal brainstem would branch out and reduce central response speed and possibly also temporal acuity. Evidence for this hypothesis is presented in Figure 25.5, taken from an experiment in which a 10-ms gap in a 70-dB background noise was presented at various lead times before the startle stimulus, and the CBA mice ($N = 167$) ranged in age from 3 to 29 months. The youngest group of mice showed the usual W-shape in the relative response, with strong inhibition at the 10-ms lead time, a substantial recovery at 15 ms, and then a second inhibitory phase beginning at 20 ms. (In rats, this second inhibitory phase is sensitive to decortication, while the first is not: Ison et al., 1991). Note how this second phase occurred progressively later with age, although the first phase was at 10 ms in all but very old mice. The lead time of maximal inhibition beyond that occurring at 10 ms was calculated for each mouse, with results seen in Figure 25.6. The means ranged from just over 20 ms in young mice to about 60 ms in old mice, and the linear increase in this function with age was very striking.

What are the behavioral changes with age on gap detection at these later lead times? At the level of the inferior colliculus, relatively few cells in the old mouse have the same high temporal acuity of those in the young mouse; also, these old cells are much slower to recover their normal level of reactivity following the gap (see Chapter 24, Figures 24.5 and 24.6). A clear age-related behavioral effect of gaps presented at lead times of 60 ms in these same CBA mice is shown in Figure 25.7, with the older mice showing reliable inhibition but with a much reduced asymptotic strength (data from Barsz et al., 2000). A threshold for gap detection was calculated for each mouse, as the shortest gap duration at which inhibition was 50% of its asymptotic. The means for each age group are given in Figure 25.8. A linear regression function provides a reasonable fit to these data, but strong evidence for an age-related loss of temporal acuity as measured by gap-detection thresholds is only apparent beyond about 18 months of age. These data are also interesting in the fact that although there were large age effects seen in ABR thresholds for tone pips, the ABR did not correlate with gap detection (O'Neill and Ison, 2000).

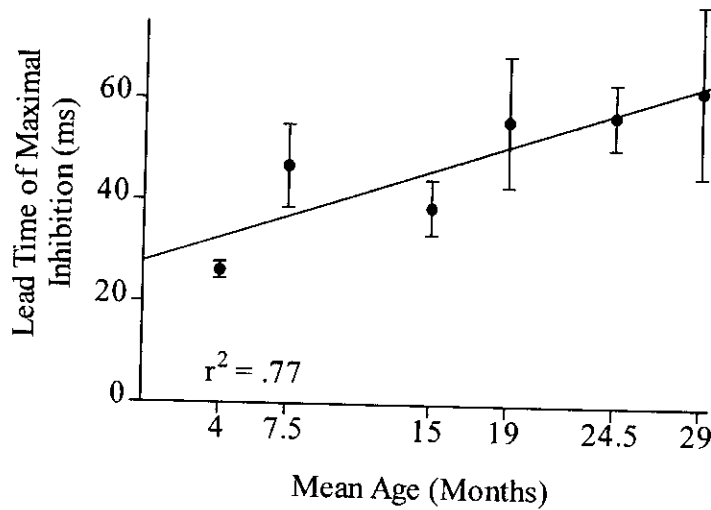


FIGURE 25.6 The mean lead time (\pm SEM) at which maximal ASR inhibition occurred, not counting the inhibition present at the 10-ms lead time, as a function of age in CBA/CaJ mice (taken from the data displayed in Figure 25.5, the values being calculated for each individual mouse).

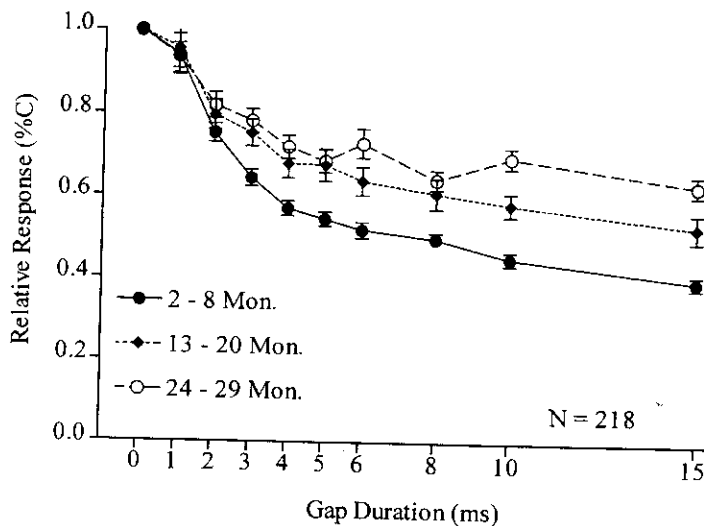


FIGURE 25.7 Mean relative ASR amplitude (\pm SEM) when the startle stimulus was preceded by gaps of various durations at an interval of 60 ms (offset of gap to onset of startle), as a function of age in CBA/CaJ mice. Inhibition developed less rapidly here with increased gap duration than it does in a noise offset condition, but the major effect of age is still to reduce the asymptotic level of inhibition.

CONCLUSIONS

The neural process that provides temporal integration of the acoustic transient that elicits the ASR must be different from that responsible for ASR inhibition by noise offset at short lead times. In turn, it is likely that noise-offset inhibition is different from inhibition by complete gaps at long lead times. Despite these differences, common outcomes do appear at each level to support the hypothesis that peripheral and brainstem mechanisms retain their threshold sensitivity to small

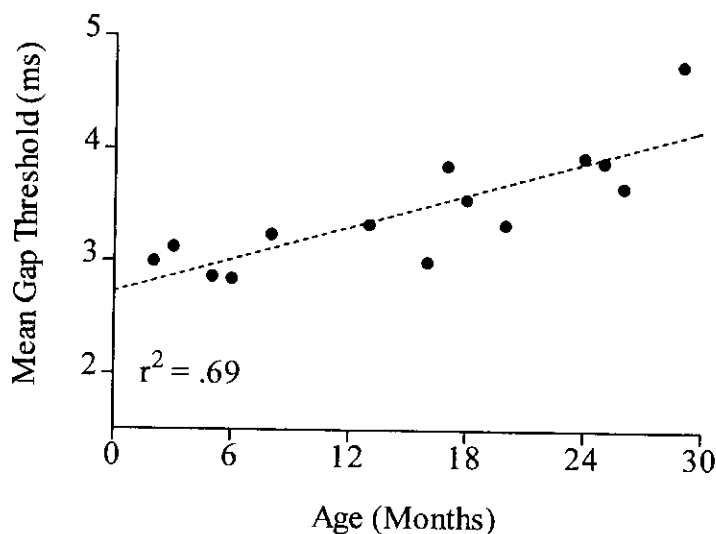


FIGURE 25.8 Mean behavioral gap thresholds as a function of age in CBA/CaJ mice, derived from the data for individual mice for which grouped age means for inhibition are presented in Figure 25.7. These threshold values were calculated for each mouse, and were defined as the minimal gap duration at which the level of inhibition was at least 50% of the maximal level of inhibition found for that mouse at any gap duration. It might be noted that a threshold of about 3 ms is very close to that obtained in young humans, and the age-related increase of about 1 ms is again close to that reported (Snell, 1997) in old human listeners.

variations in the acoustic envelope in aged mice. Moreover, the major consequence of old age appears in the lower asymptotic effect of transient input, either positive or negative. These behavioral data suggest that very brief acoustic transients are detected but are less able to generate a significant neural response, a conclusion that is consistent with the physiological data showing that there are fewer high-acuity cells in older mice. Age-related shifts in the timing of the second phase of gap inhibition and increased gap thresholds may result because the diminished neural output achieved in the early stages of neural processing spreads out through more rostral sites. This would result in delays in the time course and increases in the jitter in the input to higher processing stations. This effect must be further exacerbated by the age-related loss of transmission links from the CN to more rostral sites. There is also strong evidence for intrinsic changes at those rostral sites, for example, in the delayed recovery of aged gap-sensitive neurons in the inferior colliculus, as summarized in Chapter 24.

It has been hypothesized that the older human listeners suffer from two auditory deficits, one being a loss of audibility for certain spectral frequencies, and the second being some degree of distortion in the perception of the acoustic event. Age-related changes in sensitivity at the auditory periphery are certainly responsible for the loss of audibility. However, deficits in the neural responses to acoustic transients, which we believe are responsible for the behavioral and physiological evidence for age-related decrements in temporal acuity, seem likely to contribute to a distorted perceptual representation of the complex acoustic events that we know as speech.

ACKNOWLEDGMENT

The research described herein was supported by the USPHS, by way of Research Grant AG09524 and Center Support Grant EY01319. Correspondence should be addressed to James R. Ison, Department of Brain and Cognitive Sciences, University of Rochester, Rochester, New York 14627. Electronic mail may be sent to Ison@bcs.rochester.edu.