Age-Related Hearing Research

Snell, K.B., & Frisina, D.R. (2000). Relationships among age-related differences in gap detection and word recognition. *Journal of the Acoustical Society of America, 107,* 1615-1626. [AN 17871]

Determining the effect of age on hearing is a major thrust of our presbycusis (age-related hearing loss) research program. In this study relationships among measures of temporal acuity, speech perception, and absolute sensitivity were examined in two age groups of adult subjects (17-40 yrs. and 61-82 yrs) with normal hearing or mild hearing loss. Significant differences in gap detection thresholds and spondee-in-babble thresholds were found between the younger and older groups. Recognition of speech (spondee words) in noise background (12-talker babble) was not related significantly to audiometric thresholds in either group. Within-group comparisons suggested different patterns within the younger group than in the older group. For example, spondee in babble thresholds did not vary with age in the younger group. And within the older group of subjects, spondee in babble thresholds, gap thresholds, and audiometric thresholds were not significantly related. Gap thresholds of older subjects did not increase with age. However, both spondee in babble thresholds and two audiometric pure tone thresholds (0.25 and 2 kHz) significantly increased with age in the older group, suggesting inherent independent underlying factors since spondee-in-babble were not significantly correlated with audiometric thresholds in the older subjects.

Implications
These findings suggest that age-related changes in auditory processing occur over many decades and that the declines in word recognition in noise seen in older adults may reflect changes that begin decades earlier. That age-related changes in auditory processing apparently occur throughout the adult life span suggests that inclusion of a third group of subjects, between the traditional young and old, i.e., middle-aged, could be beneficial in future studies characterizing age-related hearing loss.

Zettel, M.L., O'Neill, W.E., Trang, T.T., & Frisina, R.D. (2001). Early bilateral deafening prevents calretinin up-regulation in the dorsal cortex of the inferior colliculus of aged CBA/CaJ mice. *Hearing Research, 158,* 131-138. [AN 1866]

We had previously demonstrated that in a part of the brain used for hearing, the auditory midbrain (inferior colliculus), a timing problem (temporal processing deficit) develops with advancing age. We discovered this by monitoring the responses of single nerve cells, and noting that their abilities to encoded timing aspects of speech information declined with age. In the present investigation, we measured the presence of calcium-binding proteins that play important roles in regulating the amount of calcium in nerve cells. The proper level of calcium is necessary for optimal nerve cell functioning, including releasing tiny packets of chemicals to stimulate other nerve cells. We found that calcium-binding protein levels change with age, and that a certain calcium regulator increases with age and depended on hearing ability, whereas other calcium regulators declined regardless of hearing.

Implications
As we search for preventative and curative biomedical interventions for age-related sensory problems, it is important to investigate neurochemical changes in the parts of the brain used for sensory processing. Here we found evidence that the brain's ability to regulate intracellular calcium in nerve cells is impaired with age, and can be co-dependent on the amount of hearing loss. As a more complete picture is obtained for the chemical changes that take place with age in parts of the brain used for sensory processing, we move closer to developing medications, dietary supplements and other biomedical interventions based upon the underlying biochemistry of nerve cell function.

Kim, S.H., Frisina, D.R., & Frisina, R.D. (2002). Effects of age on contralateral suppression of distortion product otoacoustic emissions in human listeners with normal hearing. *Audiology & Neurotology, 7*, 348-357. [AN 1874]

This study examined the effect of contralateral suppression of otoacoustic emissions in young (18-37 yrs of age), middle age (38-57 yrs of age), and old adults (58+ yrs of age) with normal auditory absolute thresholds. Three age groups were utilized to provide a continuum of adult ages as suggested in studies reported above. Otoacoustic emissions measure outer hair cell receptor function of the inner ear. Otoacoustic measures were obtained under two conditions: without contralateral input of noise and with contralateral noise. In the latter condition white noise at a mild level was presented simultaneously as the otoacoustic amplitudes were recorded in the ipsilateral ear. Contralateral suppression is attributed to activation of the brainstem medial olivocochlear (MOC) system, which has an inhibitory effect on outer hair cell amplitudes. The performance of the young group differed significantly from the middle age and old groups. Middle age and old groups did not differ suggesting reduction in MOC function begins in middle age.

Implications
Our multidisciplinary study of presbycusis attempts to describe and determine the neurological underpinnings of presbycusis. Therefore, we seek to identify and measure all facets of the auditory system. Otoacoustic emission measurements allow quantification of the integrity of the outer hair cells of the inner ear. Combining this procedure with activation of the medial olivocochlear system (MOC) of the brainstem provides a measure of an auditory mechanism whose source is central to the inner ear. This study was the first to discover that the strength of the MOC is reduced with age, the change begins in middle age (38-57 years of age), and the change in MOC function is manifest prior to a loss in inner ear hearing thresholds. This last finding suggests reduced strength of the feedback system may be a predictor of an impending sensorineural hearing loss.

Snell, K.B., Mapes, F.M., Hickman, E.D., & Frisina, D.R. (2002). Word recognition in competing babble and effects of age, temporal processing, and absolute sensitivity. *Journal of the Acoustical Society of America, 112*, 720-727. [AN 1786]

This experiment is part of a large multidisciplinary research program designed to characterize presbycusis (age-related hearing loss) and to determine its genetic and neural bases. Its specific purpose was to determine whether speech understanding in competing babble background noise is related to temporal processing as measured by the detection of

gaps in noise bursts. Fifty adults with normal or mild high-frequency hearing loss served as subjects. The results indicated that word recognition in competing babble decreased significantly with increases in babble level, age, and gap detection thresholds. These findings suggest that age and temporal processing influence speech understanding in fluctuating backgrounds in adults with normal hearing or mild high-frequency hearing loss.

Implications
Difficulty understanding speech in background noise is a major complaint of elderly listeners. These results show that adults with normal hearing or mild hearing loss perform quite well in quiet listening environments. However, most conversations take place in the presence of background noise. The relationship between temporal processing and ability to function in noisy backgrounds by elderly listeners is better understood as a result of this study. Similar studies are ongoing with animal models that enable a better understanding of the neural underpinnings of presbycusis that eventually should lead to successful forms of treatment.

Barsz, K., Ison, J.R., Snell, K.B., & Walton, J.P. (2002). Behavioral and neural measures of auditory temporal acuity in aging humans and mice. *Neurobiology of Aging, 23,* 565-578. [AN 1864]

Three experiments compared auditory temporal acuity in humans and in the behavior and single-cell neurophysiology in the brainstem inferior colliculus (IC) of mice, to establish the comparability of aging effects on temporal acuity across species, and to suggest a neural foundation. In the first experiment, psychophysical gap detection thresholds (MGT) were measured in older and younger adult listeners who were very similar in their audiograms up to 4 kHz. These MGTs were obtained in quiet backgrounds in order to duplicate the backgrounds used in the animal experiments. The effect of age on temporal acuity in quiet was similar to those previously obtained in noise backgrounds. That is, older listeners had longer MGTs than the younger listeners. Experiment 2 measured absolute thresholds for tones using the auditory brainstem evoked potential (ABR) and behavioral MGTs in old and young mice using acoustic startle reflex modification audiometry (ASR inhibition). The effect of age on temporal encoding in mice was found to be similar to those in human listeners. The purpose of experiment 3 was to obtain a neural correlate of behavioral gap detection in mice, which could hypothetically serve the same function in human listeners. In order to accomplish this, single cell responses to silent gaps occurring in noise bursts were recording from the brainstem inferior colliculus (IC) neurons in young and old CBA mice. Comparisons among the three experiments showed a remarkable similarity in mean MGTs among the young humans, 2.3 ms, young animal behavior, 2.9 ms, and young mouse physiology, 2.7 ms. In contrast, the human old, 3.7 ms, old mouse behavior, 5.0 ms, and old mouse physiology, 26.2 ms, results demonstrated a greater rate of variability in performance than is generally found in younger adult groups.

Implications
This study expanded our understanding of age-related changes in temporal processing across species, i.e., between humans and our mouse animal model. Age-related changes in MGT between-group averages and within-group variability were measured under similar conditions across experimental paradigms, and relationship between age-related changes in signal audibility and MGT were examined. In addition, the functional significance (or salience) of supra-threshold gaps was examined behaviorally and physiologically. None of these effects had been explored in previous studies. This study replicated the effects of age on mean MGT and physiological recovery as a function of gap duration. Further, it provided direct

comparisons between behavioral and neural gap detection in young and old CBA mice and psychophysical gap detection in younger and older human listeners. Together these results suggest a neural basis for previously reported age-related changes in mean MGT, and affirm the validity of making cross-species comparisons of age-related changes in temporal processing.

Chen, X, Frisina, R.D., Bowers, W.J., Frisina, D.R., & Federoff, H J. (2001). HSV amplicon-mediated neurotrophin-3 expression protects murine spiral ganglion neurons from cisplatin-induced damage. *Molecular Therapy, 3,* 958- 963. [AN 1865]

These two studies employed gene therapy techniques to determine whether we could prevent or reduce ototoxic damage to the auditory portion of the inner ear, the cochlea. Prior to exposing the cochlea to a commonly used ototoxic chemotherapeutic agent, cisplatin, we applied a trophic gene using an inactivated herpes simplex virus vector. The gene was a member of the neurotrophin family, called neurotrophin-3 (NT-3), which was previously known to be beneficial to the nerve cells that carry information from the cochlea to the brain or central auditory system. These nerve cells make up the 8th cranial nerve, also known as the auditory/vestibular nerve. We found that application of the herpes viral vector with the NT-3 gene could significantly reduce the damage caused by the cisplatin. We found this to be true when applied in culture (in vitro) and also, notably, when injected into the cochlea of adult mice, including aged mice.

Implications

Our research is ultimately aimed at curing or preventing age-related hearing loss, as well as hearing loss due to environmental factors such as loud noise and ototoxic drugs (antibiotics, chemotherapeutic agents). One strategy is to give someone exposed to These hearing-damaging agents a preventative compound, possibly utilizing gene therapy techniques, before, during or shortly after the ototoxic event to ameliorate or reduce the damage to the inner ear. The studies presented here are a noteworthy step in that direction, since they demonstrate that the gene for NT-3 is a candidate for this type of biomedical intervention aimed at improving sensory functioning.

Bowers, W.J., Chen, X., Guo, H., Frisina, D.R., Federoff, H.J., & Frisina, R.D. (2002). Neurotrophin-3 transduction attenuates cisplatin spiral ganglion neuron ototoxicity in the cochlea. *Molecular Therapy, 6,* 12-18. [AN 1873]

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Jacobson, M., Kim, S-H., Romney, J., Zhu, X., Frisina, R.D. (2003). Contralateral suppression of distortion product otoacoustic emissions declines with age: A comparison of findings in CBA mice with human listeners. ***Laryngoscope, 113*****, 1707-1713. [AN 1872]**

We had previously discovered in our human hearing testing that the auditory feedback system (efferent system), that sends regulatory information from the brain back to the ear, starts to exhibit functional declines in middle age, with severe degradations by old age. This study was aimed at investigating whether our primary experimental animal, the laboratory mouse, would also suffer from a decline of the auditory feedback system, starting in middle age. By testing the hearing of adult mice of all age groups, including tests of the strength of the auditory feedback system in mice, we found that when one corrects for the absolute lifespan of mice and men, the mice also show a decline of the feedback system starting in "mouse" middle age. Like our human discovery, the mouse feedback decline precedes other major hearing loss indicative of cochlear damage with age.

Implications
The auditory feedback system from the brain to the ear has been implicated as one of the neural mechanisms employed to reduce the masking effects of background noise on speech comprehension. Difficulty in understanding speech in acoustically noisy environments is the number one complaint of our hearing impaired population, now about 10% of the populace, including the elderly. Based upon our findings here, this feedback system may also play a critical role in maintaining the health and well being of the sensory cells (hair cells) in the cochlea over the lifespan.

Guimaraes, P., Zhu, X., Cannon, T., Kim, S-H., & Frisina, R.D. (2004). Sex differences in distortion product otoacoustic emissions as a function of age in CBA mice. ***Hearing Research, 192*****, 83-89. [AN 1871]**

It is generally the case that women have better hearing than men, at all ages, and even after correcting for the fact that men have greater exposures to ototoxic events such as loud noises. This female sensory superiority points to the possibility that it may be due to hormonal sex differences. To investigate this phenomenon in our laboratory mice, we recorded an interesting physiological index in the mouse ear canal called distortionproduct-otoacoustic emissions, DPOAEs. These emissions are actually sounds that come out of the ear, and can be recorded by a tiny microphone placed in the mouse(or human) ear canal. The greater the size (amplitude) of these emissions, sometimes called cochlear echoes, the healthier the

cochlear hair cell system is. We found that the age-related decline in these emissions was greater for male mice than females, through middle age, or through "mouse menopause." In old age, the female declines were greater, so that old male and female mice ended up with about the same hearing levels as measured by these emissions.

Implications
Understanding female/male sensory system differences is interesting and enlightening, and has implications for possible therapies. For example, it may be that a more effective hormone replacement therapy, or hormone compensation medication, could be developed in the future to improve sensory function in general, in aged females, without the negative side-effects of currently prescribed hormone therapies for post-menopausal women. In addition, sensory research on sex differences and effects of hormones will call attention to possible side effects, and hopefully be better incorporated into drug company medication development and FDA clinical trial assessments of new drug side effects.

Simon, H., Frisina, R.D., Walton, J.P. (2004). Age reduces response latency of mouse inferior colliculus neurons to AM sounds. *Journal of the Acoustical Society of America, 116,* 469-477. [AN 1870]

Single-nerve cell recordings were made in the auditory midbrain of awake (tranquilized) mice of different adult age groups. We found that responses to various sounds actually occurred earlier in time in old mice relative to young adults. A likely neural basis for this decreased response time is the faltering of a fast inhibitory neural input to these auditory midbrain nerve cells. This inhibition would normally sharpen the ability of these nerve cells to process timing features of speech and music sounds.

Implications
One of our major goals has been to identify the neural bases of age-related hearing loss, attempting to discern the "site-of-lesion." This oftentimes involves discovering what age-related neural changes take place in the inner ear, versus those that take place in the brain—the central auditory system. Single nerve cell recordings in awake mice comprise one of the most powerful means of isolating a particular neural change to a specific locus in the brain. Here we determined that the delicate interplay between neural excitation and neural inhibition becomes disrupted with age in the auditory midbrain (inferior colliculus), a subcortical portion of the brainstem auditory system. We had previously discovered that this region has an age-related decline in neural temporal processing of speech features, and in conjunction with the current study, this age-related timing problem is likely related to a lack of neural inhibition.

Tadros, S.F., Frisina, S.T., Mapes, K, Kim, S.H., Frisina, D.R., & Frisina, R.D. (2005). Loss of peripheral right-ear advantage in age-related hearing loss. *Audiology & Neurotology, 10,* 44-52. [AN 1868]

In young adults with normal hearing, the right ear is more sensitive than the left to simple sounds (peripheral right-ear advantage) and to processing complex sounds such as speech (central right-ear advantage). In this study the effects of hearing loss and aging on this auditory asymmetry were examined at both peripheral and central auditory nervous system

levels. A group of aged subjects (ages 58-76 yrs) with normal hearing (flat audiograms) were compared to a group of aged subjects (ages 55-83 yrs) with symmetric sloping audiograms (presbycusis). Audiograms and transient evoked otoacoustic emissions (TEOAE) amplitudes were used to assess cochlear function. Contralateral suppression of TEOAEs was measured to assess the medial olivocochlear brainstem efferent system. The Hearing In Noise Test (HINT; binaural speech) was conducted to assess higher central auditory function. At the cochlear (peripheral) level, the normal hearing group showed significantly higher otoacoustic emission amplitudes for the right ear compared to the left ear, which is consistent with the right-ear dominance normally seen in young adults. However, this finding was reversed in the presbycusis group that showed higher left-ear emission amplitudes. At the brainstem level, the amplitudes of TEOAE contralateral suppression were small with no significant difference found between the right and left ears in both groups. To the contrary, HINT results showed a continuous dominance of the right ear (left hemisphere) in both groups, which was consistent with previous reports showing the right hemisphere is more affected by age than the left hemisphere.

Implications
Age affects the auditory system in complex ways. Our interest is to determine the site and behavioral consequences of various disorders ranging from the peripheral spectral analyzing characteristics of the cochlea to the language dominant brains left hemisphere. Peripheral loss of right-ear advantage seemed not to have occurred at the ages used in the present study. Loss of efficiency at the brainstem level occurred in both groups suggesting the influence of age. The loss of right-ear advantage at the cochlear level was a new finding. Animal models are being used to follow up the noted differences neurophysiologically, neuroanatomically and neurochemically. Reversing these changes is the long term goal of the project. The significance of these multiple changes for hearing aid use remains to be determined.

Varghese, G.I., Zhu, X., Frisina, R.D. (in press). Age-related declines in distortion product otoacoustic emissions utilizing pure tone contralateral suppression in CBA/CaJ mice. *Hearing Research, 207*. [AN 1869]

Adult mice of different age groups had their auditory brainstem responses (ABRs) and distortion-product otoacoustic emissions (DPOAEs) measured. In addition, contralateral sounds were presented to measure the strength of the auditory efferent feedback system. Tones (single frequency) were found to be much less effective than a noise (many frequencies, wideband stimulus) in activating the efferent system. We also found that even though the sounds that activate this system may have high pitches, the main reduction in sound being processed in the inner ear is in the low pitch regions, apical areas of the cochlea.

Implications
The auditory efferent feedback system (medial olivocochlear bundle–MOC) has been implicated as one of the neural mechanisms used by the ear and brain to reduce the effects of distracting background noise. We also have evidence that it is necessary to maintain the normal health and well being of the sensory cells of the inner ear–hair cells. We and others have found that it is particularly responsive to general noises (wideband noise containing many sound frequencies). Here we found that more specific sounds, such as tones, are not nearly as effective in activating this feedback system. Most likely, this system exerts itself maximally at the low pitches because most environmental noises that reach the ears are weighted in the low pitches, so they are most in need of reduction to improve speech perception in background noise.

Tadros, S., Frisina, S.T., Mapes, F., Frisina, D.R., & Frisina, R.D. (in press). Higher serum aldosterone levels correlates with lower hearing thresholds: A possible protective hormone against presbycusis. *Hearing Research, 207*. [AN 1868]

A group of aged subjects received a comprehensive set of standard and state-of-the-art hearing tests, characterizing the nature of their hearing loss, for both the ear and brain. At the end of the hearing testing session, we obtained a blood samples from each subject and sent it to the lab for analysis of key blood values, including aldosterone levels. Aldosterone is one of the major hormones of the body for regulating blood pressure, fluid balances and sodium/potassium concentrations. All subjects were of relatively good health and had blood values within clinically normal limits. We found that there were significant correlations between the aldosterone levels and the hearing abilities, for both cochlear (inner ear) measures and central auditory processing measures for the parts of the brain used for hearing. Specifically, the higher the aldosterone levels, within the normal clinical range, the better the aged subject's hearing abilities.

Implications

Determining relations between age-related health deficits and hearing capabilities in our aged population is a major portion of our goal of fully characterizing presbycusis—age-related hearing loss. We have previously characterized the nature of this loss in aged type II diabetics and those suffering from hypothyroidism, two common ailments of aging in our society. Hormone levels can fluctuate with age, usually declining as is the case with aldosterone, so it is important to discover the effects of these hormone changes on sensory functioning the elderly. Here we determined that as blood (serum) levels of this hormone decline with age, there is an additional or accelerated age-related hearing loss, with the neural etiology located in both the inner ear and the brain. Put another way, having normal levels of aldosterone may provide a protective effect on reducing the extent or progression of presbycusis.

Note: *[AN XXXX] represents a local NTID publications designation. Please include when requesting copies of these publications.*

Note: *The articles in this section are arranged in chronological order, to show the progression of research undertaken by the International Center for Hearing and Speech Research at the National Technical Institute for the Deaf. The research reported in these publications was funded by grants from the National Institutes of Health, National Institute on Aging.*