Springer Handbook of Auditory Research

Karen S. Helfer
Edward L. Bartlett
Arthur N. Popper
Richard R. Fay *Editors*

Aging and Hearing

Causes and Consequences

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Springer Handbook of Auditory Research

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The Acoustical Society of America

On 27 December 1928 a group of scientists and engineers met at Bell Telephone Laboratories in New York City to discuss organizing a society dedicated to the field of acoustics. Plans developed rapidly, and the Acoustical Society of America (ASA) held its first meeting on 10–11 May 1929 with a charter membership of about 450. Today, ASA has a worldwide membership of about 7000.

The scope of this new society incorporated a broad range of technical areas that continues to be reflected in ASA's present-day endeavors. Today, ASA serves the interests of its members and the acoustics community in all branches of acoustics, both theoretical and applied. To achieve this goal, ASA has established Technical Committees charged with keeping abreast of the developments and needs of membership in specialized fields, as well as identifying new ones as they develop.

The Technical Committees include acoustical oceanography, animal bioacoustics, architectural acoustics, biomedical acoustics, engineering acoustics, musical acoustics, noise, physical acoustics, psychological and physiological acoustics, signal processing in acoustics, speech communication, structural acoustics and vibration, and underwater acoustics. This diversity is one of the Society's unique and strongest assets since it so strongly fosters and encourages cross-disciplinary learning, collaboration, and interactions.

ASA publications and meetings incorporate the diversity of these Technical Committees. In particular, publications play a major role in the Society. *The Journal of the Acoustical Society of America* (JASA) includes contributed papers and patent reviews. *JASA Express Letters* (JASA-EL) and *Proceedings of Meetings on Acoustics* (POMA) are online, open-access publications, offering rapid publication. *Acoustics Today*, published quarterly, is a popular open-access magazine. Other key features of ASA's publishing program include books, reprints of classic acoustics texts, and videos. ASA's biannual meetings offer opportunities for attendees to share information, with strong support throughout the career continuum, from students to retirees. Meetings incorporate many opportunities for professional and social interactions, and attendees find the personal contacts a rewarding experience. These experiences result in building a robust network of fellow scientists and engineers, many of whom become lifelong friends and colleagues.

From the Society's inception, members recognized the importance of developing acoustical standards with a focus on terminology, measurement procedures, and criteria for determining the effects of noise and vibration. The ASA Standards Program serves as the Secretariat for four American National Standards Institute Committees and provides administrative support for several international standards committees.

Throughout its history to present day, ASA's strength resides in attracting the interest and commitment of scholars devoted to promoting the knowledge and practical applications of acoustics. The unselfish activity of these individuals in the development of the Society is largely responsible for ASA's growth and present stature.

Series Preface

Springer Handbook of Auditory Research

The following preface is the one that we published in volume 1 of the Springer Handbook of Auditory Research back in 1992. As anyone reading the original preface, or the many users of the series, will note, we have far exceeded our original expectation of eight volumes. Indeed, with books published to date and those in the pipeline, we are now set for over 77 volumes in SHAR, and we are still open to new and exciting ideas for additional books.

We are very proud that there seems to be consensus, at least among our friends and colleagues, that SHAR has become an important and influential part of the auditory literature. While we have worked hard to develop and maintain the quality and value of SHAR, the real value of the books is very much because of the numerous authors who have given their time to write outstanding chapters and to our many co-editors who have provided the intellectual leadership to the individual volumes. We have worked with a remarkable and wonderful group of people, many of whom have become great personal friends of both of us. We also continue to work with a spectacular group of editors at Springer. Indeed, several of our past editors have moved on in the publishing world to become senior executives. To our delight, this includes the current president of Springer US, Dr. William Curtis.

But the truth is that the series would and could not be possible without the support of our families, and we want to take this opportunity to dedicate all of the SHAR books, past and future, to them. Our wives, Catherine Fay and Helen Popper, and our children, Michelle Popper Levit, Melissa Popper Levinsohn, Christian Fay, and Amanda Fay Sierra, have been immensely patient as we developed and worked on this series. We thank them and state, without doubt, that this series could not have happened without them. We also dedicate the future of SHAR to our next generation of (potential) auditory researchers – our grandchildren – Ethan and Sophie Levinsohn; Emma Levit; Nathaniel, Evan, and Stella Fay; and Sebastian Sierra-Fay.

Preface 1992

The Springer Handbook of Auditory Research presents a series of comprehensive and synthetic reviews of the fundamental topics in modern auditory research. The volumes are aimed at all individuals with interests in hearing research including advanced graduate students, post-doctoral researchers, and clinical investigators. The volumes are intended to introduce new investigators to important aspects of hearing science and to help established investigators to better understand the fundamental theories and data in fields of hearing that they may not normally follow closely.

Each volume presents a particular topic comprehensively, and each serves as a synthetic overview and guide to the literature. As such, the chapters present neither exhaustive data reviews nor original research that has not yet appeared in peer-reviewed journals. The volumes focus on topics that have developed a solid data and conceptual foundation rather than on those for which a literature is only beginning to develop. New research areas will be covered on a timely basis in the series as they begin to mature.

Each volume in the series consists of a few substantial chapters on a particular topic. In some cases, the topics will be ones of traditional interest for which there is a substantial body of data and theory, such as auditory neuroanatomy (Vol. 1) and neurophysiology (Vol. 2). Other volumes in the series deal with topics that have begun to mature more recently, such as development, plasticity, and computational models of neural processing. In many cases, the series editors are joined by a co-editor having special expertise in the topic of the volume.

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Volume Preface

Age-related hearing loss (ARHL) remains one of the most common chronic maladies of aging. There is increasing realization that this seemingly benign condition may have a host of negative consequences, including social isolation, depression, increased risk of falls, and cognitive decline. And as more people are living longer lives, there is heightened interest in the biological mechanisms of aging and senescence, which includes ARHL. Hence, there is interest in studying ARHL across a broad range of disciplines, including neuroscience, audiology, cognitive psychology, and epidemiology.

Since the earlier volume in the Springer Handbook of Auditory Research (SHAR) series entitled *The Aging Auditory System* (in 2009), there has been a tremendous upsurge in research in basic, translational, and clinical sciences pertinent to age-related changes in auditory system structure and function. The goal of this new volume is to provide an overview of this topic in a format that is accessible and comprehensible to a wide range of researchers interested in ARHL. The hope is that this volume will allow researchers in one area to gain a greater appreciation for research done in other areas, to facilitate the understanding of how others' research might relate to yours, and to inspire future researchers to tackle the complex questions remaining about ARHL.

The volume considers ARHL in 12 chapters that, together, provide a broad view of the topic. Chapter 1, by Karen Helfer and Edward Bartlett, provides an overview of the volume. In Chap. 2, Shinichi Someya and Mi-Jung Kim describe a range of genetic mutations that affect hearing thresholds and function.

Central nervous system changes with aging are then considered in several chapters. In Chap. 3 Kevin Ohlemiller and Christopher Spankovich review the cell types, cell components, and structural and synaptic changes in the cochlea and auditory nerve that lead to presbycusis. Josef Syka then reviews age-related changes in the auditory brainstem and midbrain in Chap. 4 while in Chap. 5 Gregg Recanzone reviews anatomical and physiological changes in the auditory cortex, centered on changes in primate rather than rodent models. Then, in Chap. 6, Kelly Harris reviews human electrophysiological measures and how they are influenced by aging.

More cognitive functions are then considered in several chapters. The focus of Chap. 7, by Frederick Gallun and Virginia Best, is on how aging influences the segregation of sound sources. The epidemiology of age-related hearing loss is covered in Chap. 8 by Jennifer Deal, Nicholas Reed, Emily Pedersen, and Frank Lin. Chapter 9, by Sandra Gordon-Salant, Maureen Shader, and Arthur Wingfield, deals with the complex issue of why older adults have difficulty understanding spoken messages.

In Chap. 10, Stefanie Kuchinsky and Kenneth Vaden cover the complex topic of neuroimaging. The focus of Chap. 11 by Larry Humes, Kathleen Pichora-Fuller, and Louise Hickson is the rehabilitation of older adults with hearing loss. Finally, while earlier chapters mostly focused on the mechanisms, diagnostics, and risk factors associated with ARHL, Chap. 12, by Robert Frisina, Carlos Cruz, Tanika Williamson, Xiaoxia Zhu, and Bo Ding, discusses the latest avenues for treatment of ARHL and technologies that may improve treatments or preclinical research into ARHL.

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Chapter 1
Listening to All Voices: Interdisciplinary Approaches to Understanding Hearing in Aging

Karen S. Helfer and Edward L. Bartlett

Abstract This chapter will introduce the reader to the purpose, content, and structure of *Age-Related Hearing Loss: Causes and Consequences*. In this book, recent advances in the study of age-related hearing loss are reviewed, including basic research with animal and human studies along with translational research. The book is broadly organized into several sections. Chapters 1, 2, 3, 4, and 5 examine age-related changes in the subcortical and cortical anatomy and physiology, drawing primarily on animal studies. Chapters 6 and 7 transition to understanding human age-related changes using electrophysiological measures. Chapter 8 places age-related hearing impairment in the context of overall health, both as an indicator and a major correlative factor in predicting health outcomes. Chapters 9 and 10 focus on behavioral and imaging changes with aging, in order to identify difficult listening situations and the cortical regions and connectivity that are most affected. Finally, Chapters 11 and 12 discuss remediation efforts using a variety of methods. Chapter 1 provides more detailed summaries of each chapter and concludes with thoughts about future directions for research on age-related hearing loss.

Keywords Aging · Auditory processing · Presbycusis

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1.1 Purpose of This Book

Age-related hearing loss (ARHL) remains one of the most common chronic maladies of aging. There is increasing realization that this seemingly benign condition may have a host of negative consequences, including social isolation, depression, increased risk of falls, and cognitive decline. As more people are living longer, there is heightened interest in the biological mechanisms of aging and senescence, including ARHL. Hence, there is interest in studying ARHL across a broad range of disciplines, encompassing neuroscience, audiology, cognitive psychology, and epidemiology.

Increased attention has focused on these areas not only in isolation but also on the intersections and interactions between them. One example of this is the nascent area of cognitive hearing science (e.g., Arlinger et al. 2009), which has contributed much to our understanding that hearing loss associated with aging has both upstream and downstream consequences.

In tandem with interdisciplinary advances at the cognitive level, there have been advances in genetics, neuroanatomy, and electrophysiology that have enabled understanding of ARHL at the cellular and subcellular levels, such as next-generation sequencing (Rehman et al. 2010; Goodwin et al. 2016), CRISPR-Cas genomic editing (Mianne et al. 2016), large-volume neuroanatomy using optical clearing (Urata et al. 2019), multichannel calcium imaging (Issa et al. 2014), multichannel electrophysiology (Panzeri et al. 2010), and optogenetic control of auditory neurons (Natan et al. 2015). These advances include not only mechanisms of neurodegeneration in the auditory system, but also the single-cell and population-level neural responses that are correlated with age-related behavioral changes, primarily in nonhuman mammalian models.

Since publication of the earlier volume in the Springer Handbook of Auditory Research (SHAR) series entitled *The Aging Auditory System* (in 2009), there has been a tremendous upsurge in research in basic, translational, and clinical sciences pertinent to age-related changes in auditory system structure and function. A PubMed search using *Aging* and *Hearing* as key words lists 2335 articles published between 2009 and 2019. The goal of this volume is to provide an overview of this topic in a format that is accessible and comprehensible to a wide range of researchers interested in ARHL. The hope is that this volume will allow researchers in one area to gain a greater appreciation for investigations in other areas, to facilitate the understanding of how others' research might relate to one's own, and to inspire future researchers to tackle the complex questions remaining about ARHL.

1.2 Chapter-by-Chapter Overview

In Chapter 2, Shinichi Someya and Mi-Jung Kim describe a range of genetic mutations that affect hearing thresholds and function. They categorize the mutations and the affected proteins in terms of different mechanisms that are critical for proper

maintenance of hearing and that decline with aging or that accelerate ARHL. These include both nuclear and mitochondrial DNA mutations. The chapter is sectioned topically by the most critical mechanisms for hearing maintenance. Control of oxidative stress and antioxidant defense systems are important for regulating adult and aging hearing. Although cell loss is not rampant with aging, there are multiple factors such as tumor necrosis factor (TNF)-α and BCL genes that control programmed cell death, or apoptosis. More typically, there is significant neurodegeneration that can be affected by β-amyloid, purinergic (ATP) receptors and estrogen receptors. Inflammatory and immune responses and regulation that are critical for healthy aging are also described. Finally, specific screens for ARHL and the candidate genes for further study are discussed.

Next, in Chapter 3 Kevin Ohlemiller and Christopher Spankovich review the cell types, cell components, structural and synaptic changes in the cochlea and auditory nerve that lead to presbycusis. They take a comparative approach, including multiple mammalian species and data from human temporal bones. In addition, different forms of presbycusis, including sensory, metabolic, and neural presbycusis, are identified, and the evidence for them in humans and animal models is presented and evaluated. Not only are the inner and outer hair cells and their cochlear afferents discussed, but the supporting cells that enable the endocochlear potential (stria vascularis) and neural cell health are discussed as well. The age-related changes are evaluated in the classical framing of Schuknecht in terms of different patterns of degeneration (Schuknecht and Gacek 1993). In addition to an analysis of the changes in cells and components that lead to presbycusis, this chapter also reviews risk factors for presbycusis.

In Chapter 4 Josef Syka reviews age-related changes in the auditory brainstem and midbrain. For aging individuals, these brain regions typically receive impoverished auditory nerve responses due to shifts in hearing thresholds and cochlear synaptopathy. In some cases, there may be compensatory activities in these circuits to restore sensitivity to changes in sounds. The chapter is laid out to describe changes in structure and function in the cochlear nucleus, superior olivary complex, olivocochlear efferents, and inferior colliculus with aging. Given the deep internal locations and small sizes of these brain structures, the findings are based primarily on rodent studies. Overall, there are only small changes in cell number, but there are more consistent changes in calcium regulation and buffers and a reduction in synaptic markers and function, especially for inhibitory synapses. Changes in age-altered circuits can be observed mainly for temporal processing rather than spectral processing, and these changes can be observed via unit electrophysiology, auditory evoked potentials, and behavior. Declines in temporal processing with age are most evident when modulation rate is fast and/or modulation depth is small.

In Chapter 5 Gregg Recanzone reviews anatomical and physiological changes in the auditory cortex, centered on changes in primate rather than rodent models. The primate cortical studies were set up in the chapter by a discussion of subcortical anatomical changes in primates with age, including changes in calcium binding proteins, similar to those described in Chapter 4. The subcortical changes could then inform interpretation of the findings for auditory cortex single unit responses,

including increases in spontaneous activity and increases in driven rates in old auditory cortex neurons. Declines in spatial processing were observed. For temporal processing, a shift in firing patterns and processing strategies is described between young and old primates. These data lay the groundwork to understand human auditory cortex studies in later chapters.

In Chapter 6 Kelly Harris provides an overview of human electrophysiological measures and how they are influenced by aging. The chapter begins with the most peripheral measures and works up through higher levels of processing. The CAP (compound action potential)/ABR (auditory brainstem response) wave I is presented as a window into how aging affects the auditory nerve, which appears to be vulnerable to degradation even after the influence of hearing loss is taken into account. Next, research on the ABR for simple click stimuli is summarized, with the idea that age-related changes in later waves of this response are less substantial than those noted for wave I, perhaps suggesting a central gain process where the neural response at central levels is still robust despite reduced input from the periphery. More significant age-related changes can be seen in the frequency following response (FFR) and when cortical auditory evoked potentials are used to assess temporal processing. One theme throughout this chapter is that age-related differences are more apparent in evoked response measures when they are elicited by complex (rather than simple) stimuli. The chapter concludes with an overview of research supporting two intriguing ideas: that training and/or musicianship may influence age-related alterations in brainstem-level and cortical-level responses (and perhaps speech recognition); and that evoked potential measures may be an early marker for cognitive decline.

The focus of Chapter 7, by Frederick Gallun and Virginia Best, is how aging influences the segregation of sound sources. The authors begin by presenting a coherent model of the processes used to segregate sounds. They make a case that deficits in source segregation could be an indicator of "central presbycusis," as segregation relies on suprathreshold processes that fall between peripheral processing and cognitive mediation. The chapter includes a thorough but concise discussion of how aging influences the processing of cues in the temporal, spectral, and spatial domains, which likely underlies problems that older adults experience with sound segregation. Next the authors summarize research on segregation ability in older listeners. The chapter concludes with the important consideration of how older adults function in listening environments more realistic than those typically used in laboratory-based experiments.

The epidemiology of age-related hearing loss is covered in Chapter 8 by Jennifer Deal, Nicholas Reed, Emily Pedersen, and Frank Lin. The chapter begins with an overview of the prevalence and incidence of hearing loss, then proceeds to describe risk factors (including genetics, exposure to noise and toxins, and cardiovascular health and lifestyle) associated with this condition. A brief tutorial on epidemiology is presented as a background for the remaining sections of the chapter, which cover the impact of hearing loss on older adults. One focus of this chapter is how hearing loss is related to cognition in older adults, with evidence provided that supports a link between cognitive decline/dementia and age-related hearing loss. Also discussed is the association between hearing loss and physical function

(mobility, activities of daily living), as well as connections between hearing loss and social isolation. The chapter concludes with information about the novel exploration of how hearing loss is related to health care utilization, providing research evidence showing that this metric is greater in older individuals with (vs. without) hearing loss.

Chapter 9 by Sandra Gordon-Salant, Maureen Shader, and Arthur Wingfield deals with the complex issue of why older adults have difficulty understanding spoken messages. The authors present the framework of a limited resource model, where age-related decline within the peripheral and central auditory systems leads to an increased need for cognitive and linguistic processing (which also are deleteriously affected by aging). The chapter begins with a summary of age-related changes in the peripheral and central auditory systems and how they impact speech perception, with a focus on alterations in temporal processing. Next is a comprehensive discussion of how aging influences the underpinnings of the processing of spoken messages (i.e., phonological and lexical analysis, working memory/attention, inhibitory ability). The chapter also covers the relevant topic of how age-related changes in working memory and hearing sensitivity interact, with the consequence that speech understanding is more effortful in older (than in younger) individuals. It concludes with two clinically relevant areas: an overview of cochlear implants in older adults and the timely issue of how individuals' language experience (specifically, in nonnative English speakers) influences speech understanding.

In Chapter 10 Stefanie Kuchinsky and Kenneth Vaden cover the complex topic of neuroimaging. The overarching premise in this chapter is that these tools can help document listening effort exerted by older adults in challenging listening environments by identifying neural regions used for various tasks. The chapter begins with a review of the benefits and limitations of various imaging methods. It then presents a thorough discussion of listening effort, including the concept of a U-shaped curve relating effort to performance, where effort is at a maximum when the task is moderately difficult and is less when the task is so hard that the individual "gives up." Data from studies using imaging in older adults to identify underlying abilities that contribute to speech understanding are summarized, including the topic areas of functional reorganization/compensation, working memory, and the various forms of attention. The authors conclude with an overview of the limitations of applying current imaging techniques to clinical practice and provide suggestions for future directions in this area, including potential uses of new techniques to identify candidates for and effects of interventions.

The focus of Chapter 11 by Larry Humes, Kathy Pichora-Fuller, and Louise Hickson is the rehabilitation of older adults with hearing loss. The authors use the new World Health Organization (WHO) International Classification of Functioning (ICF) to consider the effects of hearing loss on speech understanding, activities, and self-reported disability. This chapter provides a concise summary of subjective ways of measuring the impact of hearing problems (i.e., questionnaires) as applied both to individuals with hearing loss and to their communication partners. The authors raise the question of whether the current classification system misses individuals with milder forms of hearing loss who might be significantly impacted. Connections between hearing loss and other health conditions, including cognitive

decline, are discussed, as is how the environments in which older adults reside affect communication. Also covered is research on the efficacy of hearing aids in older adults, with attention paid to the critical issue of poor access to affordable hearing health care, and how this might be addressed going forward. The chapter ends with a summary of other types of intervention (communication education, psychological intervention to increase motivation, cognitive training, environmental modification) used to help older adults cope with hearing loss.

Previous chapters focused mostly on the mechanisms, diagnostics, and risk factors associated with ARHL. However, in Chapter 12 Robert Frisina, Carlos Cruz, Tanika Williamson, Xiaoxia Zhu, and Bo Ding discuss the latest avenues for treatment of ARHL and technologies that may improve treatments or preclinical research into ARHL. These avenues include pharmacological approaches to affect estrogen levels, potassium channels, and antioxidants, among others. The authors discuss the challenges of clinical trials and translating basic research into clinical research, as well as the difficulties in identifying appropriate patient populations where treatments may be most effective. Finally, they discuss the obstacles for developing preclinical tools, such as a drug pump for mice that can be used to test longer-term drug treatments, which would enable assessment of new drugs and combination therapies for aging hearing.

1.3 Future Directions

A theme that runs throughout this volume is that future research should focus on multidisciplinary solutions to address the many questions that remain unanswered about age-related hearing loss. The interdependency of the underlying causes and consequences of this condition (e.g., how changes in the auditory periphery lead to changes in central structures; how age-related limitations in working memory affect speech perception) suggests that our understanding of the nature of age-related hearing problems, and how those problems can be remediated, also needs to look beyond individual disciplines or sub-disciplines. Many of the complex issues regarding aging and hearing have been (and will continue to be) best addressed by studies that bring together the points of view and expertise of researchers from two or more areas. Examples of these could include how older adults compensate for age-related changes on both physiological and behavioral levels; the implications of ARHL on a societal level (including economics); and use of the same techniques for diagnostics and treatments in animal models and humans (e.g., auditory evoked potentials, functional magnetic resonance imaging [fMRI], pharmacology).

Just as there is a need to look across disciplines to understand the aging auditory system, it is also critical to look across levels of system organization. For any brain system, subcellular components are organized into specialized cell types, which interact to form circuits for signaling across multiple time scales, which interact with other circuits to form the overall nervous system that interacts with the rest of the organism to generate decisions and behaviors. Each of these levels of organization

changes dramatically over the developmental trajectory from early development to adulthood to aging and senescence. It is important to discover how the different components change and what causes those changes.

Many of these levels of organization are not amenable to study in humans, so researchers rely on animal models, typically using rodents and primates, to understand the cellular mechanisms that underlie behavioral changes. For auditory aging, animal studies allow a level of control for a known history of sound exposure, lifestyle (though it may be impoverished), and genetic background that is not possible in human studies. Furthermore, the subjects in the main rodent models are much shorter-lived than humans, such that it is possible to observe neurodegeneration that has similar characteristics to humans within a much shorter time span. This similarity means that causes of ARHL and hearing deficits associated with ARHL can be identified in animals, and treatments can be tested in humans. However, the translational route from animals to humans is not, and should not be, unidirectional. Researchers, clinicians, and patients all benefit from using human testing and observation of age-related hearing deficits to direct animal studies, as well as using findings from animal studies to drive different means of diagnostics and remediation in humans. The chapters in this book are organized to illustrate this bidirectional communication between researchers working with animal and human subjects. The hope is that this volume convinces present and future researchers of the importance of collaborative research that considers multiple points of reference.

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Chapter 2
Genetic and Molecular Aspects of the Aging Auditory System

Shinichi Someya and Mi-Jung Kim

Abstract Age-related hearing loss (AHL), or presbycusis, is the gradual loss of hearing and is characterized by poor speech comprehension in noisy conditions, impaired temporal resolution, and central auditory processing deficits. The major sites of age-related cochlear pathology typically include inner hair cells (IHCs) and outer hair cells (OHCs), spiral ganglion neurons (SGNs), and stria vascularis. The IHCs are the sensory receptors that relay their electrical response to the central auditory system through the SGNs. Postmitotic hair cells and SGNs are particularly susceptible to injury from a combination of noise exposure and oxidative damage. The blood vessels in the stria vascularis are essential for transporting oxygen into the cochlea. Therefore, age-related degeneration of one or more of these cochlear cells plays a major role in the development of AHL in both humans and animals. This chapter reviews the current literature on genetic and molecular aspects of the aging auditory system, particularly focusing on mouse genetic research from major auditory neuroscience and genetic journals.

Keywords Aging · Apoptosis · Development · Immune response · Neurodegeneration · Oxidative stress

2.1 Introduction

The overall objective of this chapter is to review the current literature on genetic and molecular aspects of the aging auditory system, particularly focusing on mouse studies. This chapter focuses on genes whose functions are involved in oxidative stress, apoptosis, neurodegeneration, development, and immune response, the conditions or cellular events that are known to be directly involved in aging and age-related diseases. Those genes and pathways that have been uncovered have significantly advanced the field of age-related hearing loss (AHL; a full list of

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Table 2.1 Abbreviations used in this chapter

ABR	Auditory brainstem response
AHL	age-related hearing loss
APP	amyloid precursor protein
Aβ	amyloid-β
CARD	caspase recruitment domain
CNS	central nervous system
CR	calorie restriction
CS	citrate synthase
ENU	*N*-ethyl-*N*-nitrosourea
ER	estrogen receptor
ESR1	estrogen receptor alpha
ESRRG	estrogen-related receptor gamma
FADD	FAS-associated death domain
γ-GCS	γ-glutamylcysteine synthetase
GDNF	glial cell-line-derived neurotrophic factor
GH	growth hormone
GST	glutathione *S*-transferase
GWAS	genome-wide association study
IGF-1	insulin-like growth factor-1
IHC	inner hair cell
OHC	outer hair cell
PCR	polymerase chain reaction
PGR	progesterone receptor
PIP3	phosphatidylinositol 3,4,5-trisphosphate
PTEN	phosphatase and tensin homolog
ROS	reactive oxygen species
SGN	spiral ganglion neurons
TCA	tricarboxylic acid
TNF	tumor necrosis factor
XIAP	X-linked inhibitor of apoptosis

abbreviations used in this chapter is provided in Table 2.1) and contributed to the understanding of the molecular mechanisms underlying cochlear aging and both early-onset and late-onset AHL in humans.

2.2 Oxidative Stress

2.2.1 Generation of Reactive Oxygen Species by the Mitochondrial Electron Transport Chain

It is estimated that approximately 90% of intracellular reactive oxygen species (ROS) are continuously generated as a by-product of mitochondrial respiration metabolism during the generation of ATP (Beckman and Ames 1998;

Evans and Halliwell 1999). The production of superoxide (O^{2-}), one of the major ROS, is thought to occur at two electron transport chain sites in mitochondrial respiration: Complex I (NADH dehydrogenase) and Complex III (ubiquinone-cytochrome *c* reductase), but under normal metabolic conditions, Complex III is thought to be the main site of superoxide production. An early study has shown that overexpressing the antioxidant gene superoxide dismutase 2 (*Sod2*) significantly increases longevity in *Drosophila* (Sun et al. 2002). In mice, overexpressing a mitochondrially targeted catalase gene moderately increases lifespan and delays the development of AHL (Schriner et al. 2005; Someya et al. 2009).

2.2.2 *Influence of Aging on Antioxidant Defense*

Cellular components such as DNA, proteins, and lipids are protected against ROS by an interacting network of antioxidant enzymes (Evans and Halliwell 1999; Balaban et al. 2005). For example, mitochondrial SOD2 converts superoxide into hydrogen peroxide, which in turn is decomposed to water and oxygen by peroxiredoxin or glutathione peroxidase. These antioxidant defense enzymes and proteins work with each other to protect key cellular components such as DNA from ROS-induced damage over the course of the lifetime. However, the antioxidant defense system does not keep pace with the age-related increase in ROS production, and hence the balance between the antioxidant defenses and ROS production shifts progressively toward a more pro-oxidant state during aging (Balaban et al. 2005).

2.2.3 *Influence of Aging on* Gpx6, Txnrd1, Idh1, *and* Hspb1 *Expression in Cochlea*

To investigate the association between cochlear antioxidant defense and AHL, Frisina and colleagues examined the expression of antioxidant-related genes in the cochlea of CBA/CaJ mice, a model of late-onset AHL, at various ages by DNA microarray (Tadros et al. 2014). The authors found that middle-aged mice with normal hearing, old mice with mild AHL, and old mice with severe AHL showed large-fold changes in gene expression of four antioxidant-related genes: glutathione peroxidase 6 (*Gpx6*), thioredoxin reductase 1 (*Txnrd1*), isocitrate dehydrogenase 1 (*Idh1*), and heat shock protein beta-1 (*Hspb1*) when compared to young mice with normal hearing: GPX6 catalyzes the reduction of hydrogen peroxide (Evans and Halliwell 1999); cytosolic IDH1 catalyzes the conversion of isocitrate to α-ketoglutarate and $NADP^+$ to NADPH (Reitman and Yan 2010); cytosolic TXNRD1 is a member of the thioredoxin antioxidant defense system that reduces oxidized thioredoxin 1 to reduced thioredoxin 1 and NADPH to $NADP^+$ (Evans and Halliwell 1999); HSPB1 (HSP27) is a member of the heat shock protein family that, in response to stress, acts as a molecular chaperon to inhibit apoptosis

by inhibiting cytochrome-*c*-mediated activation of caspases in the cytosol (Bruey et al. 2000). The results showed that the expression of *Gpx6* was upregulated, while the expression of *Txnrd1* was downregulated in the cochlea of middle-aged mice with normal hearing, old mice with mild AHL, and old mice with severe hearing loss, suggesting a decline in the activities of TXNRD1 is involved in cochlear aging.

2.2.4 Role of NRF2 in Reducing Oxidative Stress in Cochlea

The transcription factor NRF2 regulates transcription of genes encoding phase II detoxification enzymes such as glutathione *S*-transferase (GST) and antioxidant enzymes such as γ-glutamylcysteine synthetase (γ-GCS), the rate-limiting enzyme in glutathione biosynthesis (Kobayashi and Yamamoto 2005; Leiser and Miller 2010). Interestingly, primary skin-derived fibroblasts from long-lived Snell dwarf mutant mice exhibited elevated levels of *Nrf2*, higher levels of glutathione, and resistance to plasma membrane lipid peroxidation, while treatment of the dwarf-derived fibroblasts with arsenite, an inducer of NRF2 activity, and increased resistance to paraquat and hydrogen peroxide compared to untreated cells (Leiser and Miller 2010). Hoshino and colleagues (Hoshino et al. 2011) examined the roles of *Nrf2* in AHL using *Nrf2* knockout mice. There were no differences in auditory brainstem response (ABR) thresholds between young BDF1 control and $Nrf2^{-/-}$ mice. However, middle-aged $Nrf2^{-/-}$ mice displayed significantly higher ABR thresholds compared to age-matched control mice. This was associated with reduced numbers of hair cells and spiral ganglion neurons (SGNs) in the cochlea of middle-aged $Nrf2^{-/-}$ mice compared to age-matched control mice. These results suggest that NRF2 or NRF2-induced antioxidant defense plays a neuroprotective role against ROS in cochlea during aging.

2.2.5 Role of IDH2 in the Mitochondrial Antioxidant Defense in Cochlea

Mitochondrial IDH2 participates in the tricarboxylic acid (TCA) cycle and catalyzes the conversion of isocitrate to α-ketoglutarate and $NADP^+$ to NADPH in the mitochondrial matrix (Reitman and Yan 2010). IDH2 also plays a role in protecting mitochondrial components from oxidative stress by supplying NADPH to both glutathione reductase and thioredoxin reductase 2 within the mitochondrial matrix. White and colleagues (White et al. 2018) investigated the effects of *Idh2* deficiency on age-related cochlear pathology and AHL using $Idh2^{+/+}$ (WT) and $Idh2^{-/-}$ mice. The authors found that old male $Idh2^{-/-}$ mice displayed increased ABR thresholds, increased wave I latency, and decreased wave I amplitude compared to age-matched

WT mice. This was accompanied by increased oxidative DNA damage, increased apoptotic cell death, and profound loss of SGN and HCs in the cochlea of old *Idh2*$^{-/-}$ mice. Loss of *Idh2* also resulted in a decreased NADPH redox state and decreased activity of TXNRD2 in the mitochondria of the inner ear of young mice. These results suggest IDH2 functions as the principal source of NADPH for the mitochondrial thioredoxin antioxidant defense and plays an essential role in protecting cochlear hair cells and neurons against oxidative stress during aging.

2.2.6 Role of SIRT3 in Enhancing the Mitochondrial Antioxidant Defense in Cochlea under Calorie Restriction

Sirtuins are a family of NAD^+-dependent protein deacetylases that extend life span in worms and flies (Finkel et al. 2009). SIRT3, a member of the mammalian sirtuin family, is localized to mitochondria and regulates levels of ATP and the activity of Complex I of the electron transport chain (Ahn et al. 2008). Calorie restriction (CR) or reducing food consumption by 25%–60% without malnutrition, consistently extends life span and delays the onset of age-related diseases in a variety of species, including rodents and monkeys (Kaeberlein 2010; Burnett et al. 2011). Previous studies have shown that CR increases protein levels of SIRT3 in primary mouse cardiomyocytes, while overexpression of *Sirt3* protects these cells from oxidative stress–induced cell death (Sundaresan et al. 2008), suggesting a role of SIRT3 in aging retardation under CR conditions. A subsequent study investigated the effects of *Sirt3* deficiency on cochlear pathology and AHL under control diet and calorie restricted conditions using *Sirt3*$^{+/+}$ (WT) and *Sirt3*$^{-/-}$ mice (Someya et al. 2010). Aging resulted in elevated ABR hearing thresholds in middle-aged WT mice under control diet, while CR delayed the development of AHL in WT mice. However, CR did not delay AHL in *Sirt3*$^{-/-}$ mice. In agreement with the ABR test results, CR reduced oxidative DNA damage and SGN degeneration in the cochlea of middle-aged WT mice, but not *Sirt3*$^{-/-}$ mice. Under CR conditions, SIRT3 also activated IDH2, leading to increased NADPH levels and glutathione redox state in mitochondria. These results suggest that SIRT3 acts as a key player in enhancing the mitochondrial glutathione antioxidant defense system in cochlea and slowing the development of AHL under CR conditions.

2.2.7 Role of SIRT1 in the Antioxidant Defense in Cochlea

Although earlier studies showed that sirtuins extend life span in lower organisms (Finkel et al. 2009), subsequent studies revealed that overexpression of *Sir2* does not increase life span when compared with a genetically standardized control strain

in worms and flies, and that *Sir2* is not required for life span extension by CR (Kaeberlein 2010; Burnett et al. 2011). Li and colleagues have also shown that inhibition of *Sirt1*, a member of the mammalian sirtuin family, protected rat cortical neurons against oxidative stress (Li et al. 2008), suggesting that sirtuins can also accelerate aging. Han and colleagues (Han et al. 2016) examined the effects of *Sirt1* deficiency on cochlear pathology and hearing using $Sirt1^{+/+}$ (WT) and $Sirt1^{-/-}$ mice. The authors found that aging resulted in elevated ABR hearing thresholds in middle-aged WT mice. However, middle-aged $Sirt1^{-/-}$ male mice displayed significantly lower ABR thresholds compared to age-matched WT mice. This was associated with reduced oxidative damage and reduced degeneration of cochlear hair cells (HCs) and SGNs in middle-age $Sirt1^{-/-}$ mice. In mouse inner ear cell lines, *Sirt1* knockdown increased cell viability, increased acetylation status of Foxo3a, and increased activity of catalase under oxidative stress conditions. These results suggest that SIRT1 may promote AHL through suppressing FOXO3a-mediated oxidative stress resistance or catalase activity in mouse cochlea.

2.2.8 Role of Citrate Synthase in the Maintenance of Mitochondrial Function in Cochlea

Citrate synthase (CS) participates in the TCA cycle and catalyzes the synthesis of citrate from oxaloacetate and acetyl coenzyme and generates NADH and FADH2 for oxidative phosphorylation in the mitochondrial matrix (Suissa et al. 1984). C57BL/6 and A/J mice carry the same *ahl* variant of the *Cdh23* gene and exhibit early onset AHL. However, these two inbred strains exhibit dramatically different time courses of AHL: the hearing loss of A/J mice occurs much earlier than that of C57BL/6 and exhibits a rapid loss of hair cells, beginning at the basal turn and progressing toward the apex (Zheng et al. 2009), indicating that additional genetic factors must contribute to the accelerated rate of hearing loss in A/J mice. Two such factors have been identified by Johnson and colleagues: a DNA variant of the mitochondrial tRNA arginine (*mt-Tr*) gene (Johnson et al. 2001) and a missense mutation of the citrate synthase gene (*Cs*) (*ahl4*) (Zheng et al. 2009; Johnson et al. 2012). Johnson et al. (2012) also mapped *ahl4* by analysis of a new linkage backcross and determined a nucleotide variant (H55N) in exon 3 of *Cs* as the underlying cause of *ahl4*-related hearing loss. A subsequent study showed that siRNA knockdown of *Cs* reduced oxygen consumption rates, ATP production level, and increased superoxide formation, resulting in apoptotic cell death in human kidney cell lines (Cai et al. 2017), implicating that a decline in citrate synthase activity can lead to increased oxidative stress and mitochondrial dysfunction.

2.2.9 Role of Mitochondrial DNA Mutations in Cochlear Aging

As discussed in Sect. 2.2.8, A/J mice also carry a variant of the mitochondrial arginine tRNA gene (*mt-Tr*) that contributes to early-onset AHL. An earlier study showed mouse NIH3T3 cell lines carrying mitochondrial DNA (mtDNA) with the A/J strain variant of *mt-Tr* exhibited reduced mitochondrion respiration capacity and increased ROS production compared to control cell lines carrying wild-type mtDNA (Moreno-Loshuertos et al. 2006). In agreement with these reports, mice carrying a mutation (D257A) that disrupts the exonuclease domain of the mtDNA polymerase γ exhibit a variety of premature aging phenotypes, including hair loss and graying, reduced life span, and early-onset AHL compared to age-matched wild-type mice (Kujoth et al. 2005; Someya et al. 2008). Moreover, young mtDNA mutator ($Polg^{D257A/D257A}$) mice displayed a 200- to 500-fold increase in mtDNA point mutations in the brain, heart, and inner ear (Vermulst et al. 2007; Kim et al. 2019), while mtDNA deletions accumulated at an accelerated rate (a 7- to 11-fold increase) in the brain, heart, and inner ear of mtDNA mutator mice with age. These results suggest that mtDNA mutations contribute to premature aging phenotypes in mtDNA mutator mice.

2.3 Apoptosis

2.3.1 Two Major Pathways of Apoptosis

An apoptosis program is thought to play a key role in aging and age-related diseases (Mattson 2000; Someya and Prolla 2010). Neuronal death also contributes to the symptoms of many neurological disorders, including Alzheimer's disease, Parkinson's disease, Huntington's diseases, stroke, and amyotrophic lateral sclerosis (Mattson 2000). Apoptosis can occur through two major pathways: the extrinsic pathway is a sensor for extracellular signals and is initiated through the ligation of tumor necrosis factors (TNFs). The intrinsic pathway or the mitochondrial pathway senses intracellular damage and is initiated when the outer mitochondrial membrane loses its integrity (Lindsten et al. 2000; Youle and Strasser 2008). The mitochondria apoptosis pathway is regulated by BCL-2 family members (Youle and Strasser 2008). Of the BCL-2 family members, the pro-apoptotic proteins BAX and BAK play a central role in promoting mitochondria-mediated apoptosis (Lindsten et al. 2000). Lindsten and colleagues (Lindsten et al. 2000) have shown that $Bak^{-/-}$ mice do not exhibit any gross abnormalities or developmental defects. However, the majority of mice lacking both *Bak* and *Bax* died prenatally with fewer than 10% of the mutants surviving into adulthood. Those $Bax^{-/-}$–$Bak^{-/-}$ mice displayed multiple developmental defects such as accumulation of excess cells within both the central nervous and hematopoietic systems, indicating that BAX and BAK play central roles in the regulation of apoptosis during development and tissue homeostasis. In

the extrinsic pathway, TNF is a cell signaling protein involved in immune and inflammatory responses and a major mediator of extrinsic apoptosis (Chen and Goeddel 2002; Chau et al. 2004). Activation of TNF signaling is involved in the pathogenesis of a wide spectrum of diseases, including diabetes, cancer, osteoporosis, and autoimmune diseases such as multiple sclerosis and inflammatory bowel disease (Chen and Goeddel 2002). TNF signals through two distinct cell surface receptors, TNF-R1 and TNF-R2. Of these receptors, TNF-R1 initiates the majority of TNF's apoptotic activities.

2.3.2 Influence of Aging on Apoptotic Genes in Cochlea

To investigate the association between apoptosis, cochlear aging and AHL, Frisina and colleagues (Tadros et al. 2008) examined by DNA microarray and real-time polymerase chain reaction (PCR) the expression of 318 apoptotic genes in the cochlea of CBA/CaJ mice at various ages: young mice with normal hearing, middle-aged mice with normal hearing, old mice with mild hearing loss, and old mice with severe hearing loss. Of the 318 apoptotic genes, 8 showed significant differences in mRNA expression that were validated by real-time PCR: activating transcription factor3 (*Atf3*), B cell leukemia/lymphoma 2 (*Bcl2*), Bcl2-like 1 (*Bcl2l1*), caspase4 (*Casp4*), Calpain 2 (*Capn2*), dual specificity phosphatase 9 (*Dusp9*), tumor necrosis factor receptor superfamily member 12a (*Tnfrsf12a*), and TNF superfamily member 13b (*Tnfsf13b*). Comparing the gene expressions of middle-aged mice with normal hearing, old mice with mild hearing loss, and old mice with severe hearing loss, seven genes (*Atf3*, *Bcl2*, *Bcl2l1*, *Casp4*, *Dusp9*, *Tnfrsf12a*, *Tnfsf13b*) showed up-regulation with age and hearing loss, while six genes (*Atf3*, *Bcl2*, *Bcl2l1*, *Casp4*, *Capn2*, and *Tnfrsf12a*) showed down-regulation in the middle-aged group compared to young mice with normal hearing. In mammals, there are at least 12 BCL-2 family proteins that have either three-dimensional structural similarity or a secondary structure that is similar to BCL-2 (Youle and Strasser 2008). These apoptosis proteins exhibit a range of bioactivities, from inhibition to promotion of apoptosis. For example, while BAX and BAK promote cell death, BCL-2 and BCL-CL inhibit apoptosis. Caspases are a family of protease enzymes that play an essential role in apoptosis (Cohen 1997; Hakem et al. 1998). The caspases are present in cells as inactive proenzymes that are activated in response to apoptotic stimulation. Activation of caspases during apoptosis leads to the cleavage of a variety of cellular proteins, leading to cell death. In mitochondrial apoptosis, cytochrome *c* initiates apoptosis by inducing the formation of the CASP9/APAF1 complex that is mediated by the interaction of their respective caspase recruitment domain (CARD) (Hakem et al. 1998; Youle and Strasser 2008). CASP4 and CASP8 can associate with APAF1 and CARD (Hu et al. 1998). In the extrinsic pathway, members of the TNF receptor family recruit and activate caspase-8 through the adaptor protein FAS-associated death domain (FADD) at the cell surface, which in turn causes subsequent activation

of downstream caspases, such as caspase-3, caspase-6, or caspase-7, without any involvement of the BCL-2 family (Youle and Strasser 2008). Therefore, these apoptotic proteins may play critical roles in age-related cochlear cell death.

2.3.3 *Role of* BCL11b *in Protecting Cochlear Hair Cells Against Apoptosis*

The B-cell leukemia/lymphoma 11B gene (*BCL11B*) encodes a zinc-finger protein and acts as an antiapoptotic factor (Grabarczyk et al. 2007). Grabarczyk et al. (2007) have shown that suppression of *BCL11b* by siRNA-induced apoptosis in transformed human T-cell leukemia and lymphoma cell lines, whereas normal mature T-cell lines remained unaffected, indicating that the survival of human T-cell leukemia and lymphoma cell lines is dependent on BCL11b. Kominami and colleagues (Okumura et al. 2011) examined the effects of *Bcl11b* deficiency on age-related cochlear pathology and associated hearing loss using WT and *Bcl11b*$^{-/-}$ mice. Immunohistological analysis revealed that BCL11b was detected in the outer hair cells (OHCs), but not in inner hair cells (IHCs), supporting cells or SGNs in the cochlea of WT mice. Loss of OHCs was observed in the cochlea of young *Bcl11b* $^{-/-}$ mice, but not in WT mice. There were no significant differences in ABR thresholds between young WT and *Bcl11b*$^{-/-}$ mice. However, middle-aged *Bcl11b*$^{-/-}$ mice displayed elevated ABR thresholds compared to age-matched WT mice. These results suggest that the anti-apoptotic BCL11b plays a role in protecting cochlear OHCs during aging.

2.3.4 *Role of PTEN in Promoting Apoptotic Cell Death in Cochlea*

Phosphatase and tensin homolog (PTEN) is a lipid phosphatase that induces cell cycle arrest and mitochondrial apoptosis through inhibition of the protein kinase B (AKT) pathway, a major survival pathway activated in cancer (Myers et al. 1998; Weng et al. 2001; Zhu et al. 2006; Georgescu 2010). Sha and colleagues (Sha et al. 2010) examined the roles of PTEN, phosphatidylinositol 3,4,5-trisphosphate (PIP3), and AKT in age-related cochlear pathology and associated hearing loss using male CBA/J mice. Immunostaining analysis revealed that PIP_3 levels decreased in the IHCs, OHCs, and supporting cells with age. In contrast, levels of PTEN protein increased in the cochlea with age. Moreover, Western blotting of cochlear proteins from old mice revealed reduced levels of the phosphorylated isoforms AKT1 and AKT2 compared to young mice. These results suggest that increased levels of PTEN and/or decreased levels of PIP_3/AKT signaling may contribute to age-related loss of hair cells and hearing loss.

2.3.5 *Role of XIAP in Protecting Cochlear Hair Cells and Spiral Ganglion Neurons Against Apoptosis*

X-linked inhibitor of apoptosis (XIAP) is a member of the Apoptosis family and inhibits apoptosis by inhibiting capase-3 and caspase-7 (Eckelman et al. 2006). Wang and colleagues (Wang et al. 2010) examined the effects of *Xiap* overexpression on age-related cochlear pathology and associated hearing loss using WT and *Xiap* transgenic (Tg) mice. The authors found that young *Xiap* Tg mice exhibited significantly lower ABR thresholds compared to age-matched WT mice. Middle-aged *Xiap* Tg mice also exhibited significantly lower ABR thresholds compared to age-matched WT mice. This was associated with reduced loss of IHCs and OHCs and reduced loss of type I and type II SGNs, HC afferent dendrites, and HC efferent axons in the cochlea from middle-aged *Xiap* Tg mice. Together, these results suggest that XIAP plays a critical role in protecting cochlear hair cells and SGNs against apoptosis during aging.

2.4 Neurodegeneration

2.4.1 *Neuronal Death, Neurodegenerative Diseases, and Hidden Hearing Loss*

During development of the peripheral nervous systems, many neurons undergo apoptosis to maintain a constant size and to make way for new cells (Mattson 2000). Although most neurons survive for the lifetime of the organisms, some neurons die as a result of normal aging and/or injury. Accordingly, neuronal death is a key feature of age-related neurodegenerative disorders. For example, death of hippocampal neurons is associated with Alzheimer's disease, while death of dopamine neurons in the substantia nigra in the midbrain is associated with Parkinson's disease (Mattson 2000). The major sites of age-related cochlear pathologies typically include SGNs (Yamasoba et al. 2013): postmitotic SGNs are susceptible to injury from a combination of noise exposure, ototoxic chemicals, and oxidative damage. Hence, age-related degeneration of cochlear neurons can promote the development of AHL. To test the hypothesis that SGN degeneration plays a major role in AHL, Kujawa and colleagues (Sergeyenko et al. 2013; Kujawa and Liberman 2015) have demonstrated that degeneration of cochlear synapses precedes both hair cell loss and ABR threshold elevation in mice: synaptic counts in the IHC area decreased from 1 month of age to 3 years of age with mean age-related loss of approximately 50% across a broad range of cochlear locations. In contrast, hair cell loss was minimal until very late in life. These findings strongly suggest that cochlear synaptopathy can be widespread in ears with intact hair cell populations and normal audiograms. In humans, this type of phenomenon has been termed "hidden hearing loss" (Schaette and McAlpine 2011).

2.4.2 Role of Amyloid-β in Cochlear Neurodegeneration

A key feature of Alzheimer's disease is accumulation of amyloid plaques formed by aggregates of amyloid-β (Aβ) peptide generated by amyloid precursor protein (APP). Aβ is thought to produce neuronal toxicity through binding neuronal receptors, such as the metabotropic glutamate receptor (Lee et al. 2004). Tsuda and colleagues (Omata et al. 2016) generated transgenic mice expressing Aβ (Tg(*Math1*^{E}–*Aβ42*^{Arc})1Lt) in the hair cells and examined the role of Aβ in age-related cochlear pathology and hearing loss. Immunostaining with anti-Aβ revealed that Aβ proteins were detected in the endoplasmic reticulum, the stereocilia, and the plasma membrane of the hair cells of young Tg(*Math1*^{E}–*Aβ42*^{Arc})1Lt mice. This is in agreement with the previous reports that Aβ protein localizes to the plasma membrane, mitochondrial membrane, and endoplasmic reticulum in neurons (LaFerla et al. 2007). Young Tg(*Math1*^{E}–*Aβ42*^{Arc})1Lt mice exhibited significantly higher ABR thresholds compared to non-Tg mice. Middle-aged Tg(*Math1*^{E}–*Aβ42*^{Arc})1Lt mice also exhibited elevated ABR thresholds compared to age-matched non-Tg mice. This was associated with severe loss of hair cells and SGNs in the basal region of the cochlea from Tg(*Math1*^{E}–*Aβ42*^{Arc})1Lt/129 mice. Microtubule-associated protein tau (MAPT) is thought to play a role in the development of Alzheimer's disease (Ittner and Gotz 2011). To further investigate whether there is an interaction between Aβ and tau, double Tg mice (*Tau*;*Aβ42*^{Arc}) harboring both Tg(*Math1*^{E}–*Aβ42*^{Arc})1Lt and Tg(*Math*E–*MAPT*)1Lt were generated. Young double Tg mice exhibited severe hearing defects; ABR thresholds were significantly increased compared to non-Tg mice. Therefore, these results suggest that accumulation of Aβ can play a role in cochlear neurodegeneration and associated hearing loss.

2.4.3 Role of GIPC3 in the Protection of Spiral Ganglion Neurons

The *GIPC* (GAIP interacting protein, C terminus) genes encode a member of the GIPC family that interacts with a host of proteins that are involved in neurotransmitter, signal transduction, and vesicular trafficking (Lou et al. 2001; Booth et al. 2002). An earlier study showed that loss of *Gipc1*, another member of the GIPC family that interacts with myosin VI, resulted in a reduction in pre- and postsynaptic transmission in hippocampal neurons (Yano et al. 2006). Charizopoulou et al. (2011) identified a sequence polymorphism in the PDZ domain of *Gipc3* (343G > A) as the cause of progressive, age-related hearing loss using BLSW (*Gipc3*$^{343A/A}$) mice. Young BLSW (*Gipc3* $^{343A/A}$) showed significantly elevated ABR thresholds compared to age-matched control mice. However, middle-aged BLSW (*Gipc3* $^{343A/A}$) mice exhibited profound hearing loss that progressed from higher to lower frequencies. These results suggest that GIPC3 is required for postnatal maturation of the hair bundle and protecting cochlear hair cells and SGNs.

2.4.4 Neuroprotective Role of P2RX2 in Cochlea

The ligand-gated ion channel receptor *P2RX2* (purinergic receptor P2X2) gene encodes a member of the family of purinoceptors for ATP that functions as a ligand-gated ion channel and mediates synaptic transmission between neurons and from neurons to smooth muscle and excitatory postsynaptic responses in sensory neurons (Brake et al. 1994; North 2002). Liu and colleagues (Yan et al. 2013) investigated the role of P2RX2 in age-related cochlear pathology and associated hearing loss using male WT and *P2rx2*$^{-/-}$ mice. There were no differences in ABR thresholds between young WT and *P2rx2*$^{-/-}$ mice. However, middle-age *P2rx2*$^{-/-}$ mice displayed significantly higher ABR thresholds. Histological analysis of cochlear tissue from middle-age *P2rx2*$^{-/-}$ mice revealed significantly more loss of hair cells, supporting cells, and SGNs in the basal region compared to age-matched WT mice. Therefore, these results suggest that P2RX2 plays a neuroprotective role in cochlea during aging.

2.4.5 Role of Estrogen in the Central and Peripheral Auditory Nervous Systems

2.4.5.1 ESRRβ, *ESR2*, and ESRRγ

Sex hormones such as estrogen play an important role in the development and physiology of the CNS and are also implicated in the maintenance of normal hearing function (Anderson 1996; Hultcrantz et al. 2006). In support of this view, women with Turner syndrome, where a lack of estrogens is one of the main characteristics, commonly develop early onset of hearing loss (Stenberg et al. 2002; Hederstierna et al. 2009). *ESRRβ* also cause nonsyndromic hearing impairment in humans (Collin et al. 2008). In agreement with these reports, a decline in hearing sensitivity has been linked to menopause in humans and laboratory animals (Guimaraes et al. 2004; Hederstierna et al. 2010). In mice, mutations in genes involved in estrogen signaling such as estrogen receptor beta (*Esr2*) also cause hearing impairment in mice (Simonoska et al. 2009). *ESRRγ* gene encodes a member of the ESRR family that binds to the estrogen response element and is closely related to the estrogen receptor (ER) family (Tremblay and Giguere 2007; Giguere 2008). Dawson and colleagues (Nolan et al. 2013) generated *Esrrg* KO mice. Although most homozygous *Esrrg*$^{-/-}$ mice died in the early postnatal period, a fraction of homozygous mice survived into adulthood. Interestingly, young female *Esrrg*$^{-/-}$ mice displayed significantly higher ABR thresholds than age-matched male *Esrrg*$^{-/-}$ mice. In the central nervous system (CNS), estrogen also plays a role in the regulation of synapse formation (McEwen et al. 2001), stimulating postsynaptic density (Akama

and McEwen 2003) and protecting primary cortical neurons against glutamate toxicity (Singer et al. 1996). Therefore, these results suggest that estrogen and/or estrogen receptor signaling play an important role in protecting cochlear neurons.

2.4.5.2 WBP2

The WW domain binding protein-2 (*WBP2*) gene encodes a WW domain-binding protein that acts as a transcriptional coactivator for the estrogen receptor alpha (ESR1) and progesterone receptor (PGR) (Barth et al. 1992; Dhananjayan et al. 2006). To investigate the functional link between estrogen signaling and hearing impairment, Steel and colleagues (Buniello et al. 2016; White et al. 2013) examined the role of WBP2 in the maintenance of cochlear function using *Wbp2*$^{-/-}$ mice. At P14, there were no differences in ABR thresholds between WT and *Wbp2*$^{-/-}$ mice. However, loss of hearing sensitivity was apparent by 4–28 weeks in *Wbp2*$^{-/-}$ mice and progressively worsened. Loss of *Wbp2* also resulted in swelling of afferent terminals on the IHCs in the cochlea. This was associated with reduced mRNA expression of *Esr1*, *Esr2*, and *Pgr* in the cochlea and disruption of protein expression of postsynaptic scaffolding proteins PSD95 and SHANK3. These results suggest that WBP2 and associated estrogen signaling are essential for the maintenance of cochlear neuronal function.

2.5 Development

2.5.1 Role of Growth Hormone in Cochlear Development

Adequate amounts of growth hormone (GH) and insulin-like growth factor-1 (IGF-1), the main mediator of GH actions, are essential for normal growth and development for children (Rogol et al. 2002; Rogol 2010). Accordingly, the levels of GH and IGF-1 in circulating blood are higher early in life and begin to decline soon after physical and reproductive maturation (Bartke 2008). Consequently, blood GH levels in older adults are much lower than in younger adults. Interestingly, excessive GH levels are associated with reduced life span in humans and experimental animals, while repression of the GH/IGF-1 axis leads to lifespan extension in laboratory animals (Bartke et al. 1998; Berryman et al. 2008) Furthermore, young mice lacking the *Igf-1* gene are dwarfs and display profound hearing loss (Riquelme et al. 2010). These results suggest that GH and IGF-1 regulate both development and aging.

2.5.2 Role of RET in the Development of Cochlea and the Maintenance of Cochlear Function

The ret proto-oncogene (*RET*) encodes a transmembrane receptor and member of the tyrosine protein kinase family of proteins (Ohgami et al. 2012). RET plays an important role in cell differentiation and development of the nervous system. Glial cell-line-derived neurotrophic factor (GDNF) is one of the ligands for RET (Takahashi 2001). GDNF/RET signaling plays a crucial role in renal development and regulation of spermatogonia differentiation. Kato and colleagues (Ohgami et al. 2010) have shown previously that impairment of phosphorylation of *Ret* at tyrosine 1062 (Y1062) causes Hirschsprung's disease–linked syndromic congenital deafness in mice ($Ret^{Y1062F/Y1062F}$). Histological analysis also showed profound degeneration of SGNs associated with shrunken nuclei, discontinuous nuclear membranes, highly condensed heterochromatin, and gaps between the SGNs and the Schwann cells in the cochlea of $Ret^{Y1062F/Y1062F}$ mice. A subsequent study by the same group investigated the role of RET in age-related cochlear pathology and hearing loss (Ohgami et al. 2012). The authors found that middle-aged $Ret^{+/Y1062F}$ mice exhibited profound hearing loss. Histological analysis revealed severe degeneration of SGN associated with gaps between the SGNs and the Schwann cells, shrunken nuclei, and discontinuous nuclear membranes in the cochlea of 5-month-old $Ret^{+/Y1062F}$ mice. These results suggest that RET plays an essential role in the development of cochlea and the maintenance of cochlear function.

2.5.3 Role of ISL1 in the Development of Cochlea and Maintenance of Cochlear Hair Cells

The ISL LIM homeobox 1 (*ISL1*) gene encodes a member of the LIM-homeodomain family of transcription factors that plays an important role in regulating insulin gene expression and the development and differentiation of multiple tissues (Hobert and Westphal 2000). In the inner ear, *Isl1* is expressed in the prosensory region of otocyst, but is not expressed in postnatal auditory hair cells in mice (Huang et al. 2013). To test the hypothesis that overexpression of the developmental *Isl1* genes in mature hair cells leads to reprogramming and rejuvenation of age-related hair cell damage, Chen and colleagues (Huang et al. 2013) generated transgenic mice overexpressing *Isl1* specifically in hair cells. *Isl1*-Tg mice were viable and fertile, with normal gross appearance, and no tumors or other abnormalities were observed. Cochleas of *Isl1*-Tg mice exhibited normal morphology: hair cell bundles appeared normal. However, middle-aged *Isl1*-Tg mice displayed lower ABR thresholds at the high frequencies compared to age-matched WT mice. In agreement with the ABR results, a majority of OHCs and most IHCs were preserved in the cochlea of middle-age *Isl1*-Tg mice, while there was significant loss of OHCs and IHCs in the basal region

of the cochlea of age-matched WT mice. Moreover, significantly more synaptic ribbons remained in all regions of the cochlea from middle-age *Isl1*-Tg mice, while there was a striking reduction in the numbers of synaptic ribbons on the remaining IHCs in WT mice. Together, these results suggest that ISL1 plays an important role in the development of cochlea and maintenance of cochlear hair cells.

2.6 Immune Response

2.6.1 Aging of the Immune System

Aging can affect multiple organ systems, including the immune system: the function of the immune system declines with age, leading to increased susceptibility to infections and impaired ability to respond to vaccination, thereby accelerating the aging process (Dorshkind et al. 2009). In support of this view, individuals aged 65 years and older are more susceptible to influenza, with 80%–90% of mortalities from influenza virus infection occurring in this age group (Trzonkowski et al. 2009). Aging also results in a progressive regression in thymus size and a diminishment of thymic structure associated with immunosenescence, a degeneration of the immune system (Gui et al. 2012).

2.6.2 Neuroprotective Role of MIF in Cochlea

The macrophage migration inhibitory factor (*MIF*) gene encodes a lymphokine involved in cell-mediated immunity and inflammation (Nishihira 2000; Calandra and Roger 2003). MIF plays an important role in the regulation of macrophage function in host defense through the suppression of anti-inflammatory effects of glucocorticoids. MIF is expressed in the CNS and peripheral nerves and plays an important role in peripheral nerve regeneration and in the prevention of Schwann cell apoptosis (Fingerle-Rowson and Bucala 2001; Nishio et al. 2002). Nishizaki and colleagues (Kariya et al. 2014) examined the role of MIF in age-related cochlear pathology and hearing loss using $Mif^{-/-}$ mice. Immunostaining confirmed that MIF was observed in the spiral ligament, stria vascularis, spiral limbus, organ of Corti, Reissner's membrane, and SGCs in the cochlea of young WT mice. Although there were no differences in ABR thresholds between young WT and $Mif^{-/-}$ mice, middle-aged $Mif^{-/-}$ mice displayed significantly elevated ABR thresholds compared to age-matched WT mice. Scanning electron microscopy confirmed more profound loss of OHCs and SGNs in the cochlea of middle-aged $Mif^{-/-}$ mice compared to WT mice. Together, these results suggest that MIF plays a neuroprotective role in mouse cochlea during aging.

2.7 Candidate Genes Associated with AHL

2.7.1 Mouse Mutagenesis Screens

In order to identify genes associated with AHL, Brown and colleagues (Potter et al. 2016) conducted a large-scale genetic screen to identify mutations resulting in AHL using *N*-ethyl-*N*-nitrosourea (ENU) mutagenesis to generate pedigrees of mutagenized mice that were subjected to recurrent screens for mutant phenotypes. For the screening, male C57BL/6 mice were mutagenized with ENU and mated to C3H mice. The authors then used a high-throughput phenotyping pipeline to examine the G3 mice generated in the aging screen. In total, 105 distinct mutant lines were identified. Of these, 27 mutant lines were late-onset phenotypes across a range of physiological systems. Using whole-genome sequencing, four novel genes associated with late-onset AHL were identified: *Slc4a10, Wars2, Ptprq,* and *Zfyve26*. The solute carrier family 4, sodium bicarbonate transporter, member 10 (*Slc4a10*) gene encodes a member of the sodium-coupled bicarbonate transporters family that is involved in solute transport and pH homeostasis of neurons (Jacobs et al. 2008). At 2–6 months of age, all genotypes (*Slc4a10*$^{+/+}$, *Slc4a10*$^{+/trmb}$, and *Slc4a10*$^{trmb/trmb}$) displayed normal hearing. However, middle-aged *Slc4a10*$^{trmb/trmb}$ mice displayed significantly higher ABR thresholds at all the frequencies measured, indicating progressive late-onset hearing loss. This was associated with profound loss of OHC bundles in the cochlea of *Slc4a10*$^{trmb/trmb}$ mice. Interestingly, this large-scale screening also identified mutations leading to other age-related disorders. For example, a missense mutation (E884G) in the *Lama5* gene resulted in elevated plasma urea and creatinine levels, and with reduced plasma albumin, indicating progressive nephrotic disorder (Potter et al. 2016). A mutation in the *Acan* gene also resulted in late-onset joint deterioration and obesity with a higher percentage of fat mass. Together, these data confirm the utility of this approach and reveal a number of novel pathways involved in AHL and other age-related disorders in mice.

2.7.2 Genome-Wide Association Study

In order to identify loci associated with age-related hearing loss, Friedman and colleagues (Ohmen et al. 2014) have performed the first genome-wide association study (GWAS), in which hundreds of thousands of SNPs across the entire genome were analyzed in unrelated samples in mice. The authors of this study combined heterogeneous phenotypic data sets (ABR thresholds for 8, 16, and 32 kHz) including 226 classic inbred strains (Zheng male and female data) (Zheng et al. 1999, 2009), 387 N2 backcross mice (male and female data) from the *ahl8* mapping study (Johnson et al. 2008), and 324 mice from the Hybrid Mouse Diversity Panel (Bennett et al. 2010). This approach identified five genome-wide significant loci: *ahl* (*Cdh23*), *ahl4* (*Cs*), *ahl5* (*Gipc3*), *ahl8* (*Fscn2*), and *Gpr98*. Of these genes, *GPR98* has been associated with Usher syndrome, the most common form of hereditary syndrome that affects both hearing and vision in humans (Aparisi et al. 2014).

2.8 Recommendations for Future Research and Concluding Remarks

2.8.1 Gender Bias

This chapter reviewed the current literature on genetic and molecular aspects of AHL, particularly focusing on genes whose functions are involved in oxidative stress, apoptosis, neurodegeneration, development, and immune response, the conditions or cellular events that are known to be directly involved in aging and age-related diseases. Table 2.2 summarizes the genes that have been discussed. In the course of this chapter, we have identified various experimental approaches that could be adapted and improved in designing further aging studies using mice as a model.

Of the publications that were discussed in this chapter, 0% used females only, 21% used males only, and 58% did not indicate the sex of the animals used (unknown). Thus, it appears that sex bias is present in basic AHL research for the manuscripts screened. Given that females lose hearing more slowly than males (Pearson et al. 1995; Lin et al. 2011) and live longer than males (Austad 2006; Austad and Fischer 2016), equal inclusion of both male and female animals in basic cochlear aging and AHL research is critical for understanding the mechanism underlying aging, AHL, and gender differences in AHL in humans. Second, for basic AHL research, special attention should be paid to studying cochlear aging and AHL using C57BL/B6 mice as an AHL model because unlike humans, male C57BL/B6 mice live longer than female C57BL/B6 mice (Yuan et al. 2009), while female C57BL/B6 lose hearing more rapidly than male C57BL/B6 (Henry 2004). The CBA/CaJ strain might be a better model for studying cochlear "normal" aging and late-onset AHL because female CBA/CaJ mice live longer than male CBA/CaJ mice (Festing and Blackmore 1971; Harrison 2019) and lose hearing more slowly than male CBA/CaJ mice (Guimaraes et al. 2004; Henry 2004).

2.8.2 Genetic Background

Most of the mutant lines discussed in this chapter were derived from ES cells that were originated from 129 substrains. There are a number of 129 substrains that exhibit extensive genetic variations due to admixtures with other strains during their derivations and subsequent genetic divergence (Simpson et al. 1997). In agreement with this report, 129P1/ReJ mice carry the *Cdh23*^{753A} allele, while 129S1/SvlmJ carry the *Cdh23*^{753G} allele (Johnson et al. 2006). Therefore, special attention should be paid to addressing the possible modifying effects that different 129 substrain backgrounds might have on hearing assessments of mutants on a mixed background of C57BL/6J and 129 substrain or even on a C57BL/B6 background if the mutant line was derived from ES cell lines. To address this concern, confirming that both

Table 2.2 Genes identified for AHL phenotypes in 2010–2018 and discussed in this chapter

Function	Gene	Mouse/ background	Sex	Age of ABR testing (months)	Reference
Oxidative stress	*Gpx6*, *Txnrd1*, *Idh1*, *Hspb1*	CBA/CaJ	Both	4, 12, 28, 31	Tadros et al. (2014)
	Nrf2	BDF1	Unknown	3, 6, 11	Hoshino et al. (2011)
	Idh2	CBA/CaJ	Males	5, 24	White et al. (2018)
	Sirt3	C57BL/6J	Males	2, 12	Someya et al. (2010)
	Sirt1	C57BL/6	Males	3, 12	Han et al. (2016)
	Cs (ahl4)	C57BL/6J, A/J	Unknown	Various ages (1–14)	Johnson et al. (2012)
Apoptosis	*Atf3*, *Bcl2*, *Bcl2l1*, *Casp4*, *Capn2*, *Dusp9*, *Tnfrsf13b*, *Tnfrsf12a*	CBA/CaJ	Both	4, 12, 28, 31	Tadros et al. (2008)
	Bcl11b	C57BL/6, BALB/c	Unknown	Various ages (1–9)	Okumura et al. (2011)
	PTEN	CBA/J	Males	3, 18	Sha et al. (2010)
	XIAP	C57BL/6J	Unknown	2, 6, 10, 12, 14	Wang et al. (2010)
Neurodegeneration	*Amyloid-β*	C57BL/6, C57BL/6; 129/SvJ	Both	2, 3, 4, 5, 6, 7, 8	Omata et al. (2016)
	Gipc3 (ahl5)	Black Swiss, NIH Swiss	Unknown	Various ages (1–13)	Charizopoulou et al. (2011)
	P2RX2	C57BL/6J	Unknown	3, 17	Yan et al. (2013)
	Wbp2	C57BL/6N	Both	1, 4, 7, 11	Buniello et al. (2016)
Development	*c-Ret*	C57BL/6	Unknown	1, 4, 10, 14	Ohgami et al. (2012)
	Isl1	C57BL/6J	Unknown	3, 6, 12, 17	Huang et al. (2013)
Immune response	*Mif*	BALB/c	Unknown	1, 3, 6, 9, 12, 18	Kariya et al. (2014)
Candidate genes associated with AHL	*Cdh23 (ahl)*, *Cs (ahl4)*, *Gipc3 (ahl5)*, *Fscn2 (ahl8)*, *mt-tr (Gpr98)*	Various strains	Unknown	Various ages (1–10)	Ohmen et al. (2014)
	Slc4a10, *Wars2*, *Ptprq*, *Zfyve26*	C3H.Pde6b+; C57BL/6J, C3H.Pde6b+	Unknown	Various ages (2–12)	Potter et al. (2016)

wild-type and mutant mice are homozygous for the recessive AHL-susceptibility allele *Cdh23*^{753A} is critical for studying early-onset AHL in a mutant line on a C57BL/6 background. In addition, confirming that both wild-type and mutant mice have the same WT *Cdh23* genotype (*Cdh23*$^{753G/753G}$) is critical for studying late onset AHL in a mutant line on a CBA/CaJ background.

2.8.3 Age at ABR Testing

In humans, AHL typically develops slowly and late in life during normal aging (Pearson et al. 1995; Lin et al. 2011). Hence, use of mouse models of late-onset AHL such as CBA/CaJ may be ideal for studying late onset AHL in humans for the following reasons: first, CBA/CaJ mice display late onset AHL starting at 18–20 months of age (Guimaraes et al. 2004). Mice 18–24 months old are considered "old" and are equivalent to 56–69 years old in humans (Hagan 2017). This is important because AHL is a common feature of age-related conditions in older adults, but not in middle-aged adults. Second, in most AHL studies discussed in this chapter, C57BL/6 mice or mutants on a C57BL/6 background were used. In these studies of early-onset AHL, ABR testing was conducted at 10–15 months of age. Mice 10–15 months old are considered "middle-aged" and are equivalent to 38–47 years old in humans. Therefore, special attention should be paid in interpreting the results of age-related cochlear pathologies and AHL as aging phenotypes using middle-aged mice, because mice 10–15 months old are "not old" and do not exhibit common age-related conditions. More importantly, in general, most middle-aged individuals do not develop severe age-related disorders.

2.8.4 Concluding Remarks

In summary, AHL is a multifactorial condition involving interactions between aging, genetics, and epigenetics. Therefore, it is highly unlikely that a single gene or single pathway regulates the normal aging process in cochlea. Rather, multiple genes and multiple pathways contribute to the development of AHL over the course of the lifetime. Figure 2.1 summarizes the genes and pathways that have been uncovered. During aging, oxidative stress increases, triggering apoptotic cell death and associated neurodegeneration in the cochlea. The function of the immune system also declines with age, leading to increased susceptibility to oxidative stress, thereby accelerating the aging process. Developmental defects also directly cause cochlear neurodegeneration, leading to hearing loss. These findings have significantly advanced the field of age-related hearing loss and contributed to the under-

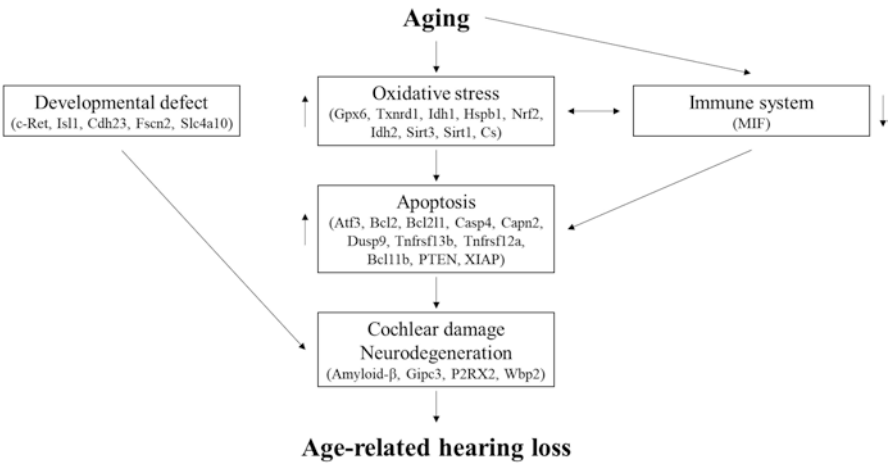

Fig. 2.1 A potential model of the development of age-related hearing loss. During aging, oxidative stress increases, triggering apoptotic cell death and associated neurodegeneration in the cochlea. The function of the immune system also declines with age, leading to increased susceptibility to oxidative stress, thereby accelerating the aging process. Developmental defects also directly cause cochlear neurodegeneration, leading to hearing loss

standing of the molecular mechanisms underlying cochlear aging and both early-onset and late-onset AHL.

Compliance with Ethics Requirements Shinichi Someya and Mi-Jung Kim declare that they have no conflicts of interest.

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Chapter 3
The Aging Cochlea and Auditory Nerve

Kevin K. Ohlemiller and Christopher Spankovich

Abstract This chapter applies a comparative approach to understanding of age-related hearing loss, or presbycusis. Research in animals reveals all forms of presbycusis described by Schuknecht and points to underlying mechanisms for further study in humans. While most humans and animals exhibit mixed pathology, testing a variety of animal models can help establish cause-and-effect, as well as which pathologies tend to coincide, and why. Small rodent models have life spans of 3 years or less, facilitating the study of age-associated pathology in a compressed timeframe. Some inbred varieties carry progressive hearing loss alleles that "accelerate" aging, although this approach has limitations. Most animal models resemble sensory presbycusis, showing exaggerated high-frequency hearing loss and outer hair cell loss. Some of the underlying genes and gene types, gleaned mostly from mouse models, overlap with suggested human risk genes. Gerbils and some inbred mouse strains exhibit strial presbycusis, which has proven particularly difficult to diagnose clinically. These models confirm and extend key principles from human research, although no "pro-strial presbycusis genes" have been identified. Although essentially all humans and animals lose cochlear afferent synapses and neuronal somata with age, only a subset of cases and models qualify for a label of neural presbycusis (>50% neural soma loss with minimum hair cell loss). Recent animal studies suggest that mild noise exposure can produce neural presbycusis-like pathology, but this has not yet been proven to occur in humans. Human and animal work indicates that aging-as-cumulative injury can account for many observations in presbycusis. Modifiable and nonmodifiable risk factors are also considered.

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3.1 Introduction

This chapter focuses on presbycusis, a broad term for age-related hearing changes that include both threshold elevation and suprathreshold hearing difficulties (Glorig et al. 1957). While the term presbycusis encompasses both peripheral and central pathology, this chapter emphasizes peripheral pathology and animal research that has shed light on the clinical condition. A problem unique to sensory epithelia (organ of Corti, retina) is the potential mismatch between energy in the stimulus and the ability of the organ to convert or dissipate that energy. Intense stimuli (loud sounds, bright light) may exceed the ability of sensory cells to moderate their input or carry out self-repair. Thus, age-related changes are commonly conceived as facets of cumulative mechanical and biochemical injury. For this reason, it has been difficult to separate "pure" aging effects from the effects of cochlear injury. Moreover, there appears to be much overlap between the putative biochemistry of sensory injury and sensory aging, as well as overlap in the discussion of how to mitigate their effects. Indeed, both central and peripheral aging effects likely represent cellular injury, with the overall presentation of presbycusis reflecting the interplay of separate injury to cochlea and brain.

3.2 The Importance of Animal Models

Much of what is understood about presbycusis derives from animal studies. Human auditory function is accessible using methods such as psychoacoustic testing, auditory brainstem responses (ABR; a full list of abbreviations used in this chapter is provided in Table 3.1), distortion product otoacoustic emissions (DPOAE), and steady-state responses. In humans, one cannot control for genetic variation or noise/ototoxin exposure, and the quality of histological specimens is often limited. In laboratory animals, by contrast, one can control for these variables through appropriate model choices and experimental design. In the hearing sciences, aging animal models have included primarily guinea pigs (*Cavia porcellus*), gerbils (*Meriones unguiculatus*), chinchillas (*Chinchilla* sp.), mice (*Mus musculus*), rats (*Rattus norvegicus*), as well as rhesus macaques (*Macaca mulatta*). All commercial rodent models feature some degree of inbreeding and genetic standardization. This standardization reaches its apotheosis in inbred mice and rats (Ohlemiller et al. 2016), which nearly eliminates genetic variability within a strain. Parallel genetic analysis of hearing loss in humans and mice has greatly sped up the pace of discovery, so that

Table 3.1 Abbreviations used in this chapter

ABR	auditory brainstem responses
ACNS	auditory central nervous system
AHEI-2010	Alternative Healthy Eating Index-2010
AMED	Adherence to the Mediterranean Diet
DASH	Dietary Approaches to Stop Hypertension
DPOAE	distortion product otoacoustic emissions
EP	endocochlear potential
GWAS	genome-wide association studies
HEI	Healthy Eating Index
IHC	inner hair cell
NHANES	National Health and Nutrition Examination Survey
OHC	outer hair cell
SIN	speech-in-noise
SP	summating potential
SR	spontaneous firing rate
TTS	temporary threshold shift
USDA	U.S. Department of Agriculture

a suspected deafness gene in humans can be "knocked out" in a mouse, confirming its role in hearing and the type of problem it may cause. As risk alleles of particular human genes are identified, these can now be generated in nearly any type of animal model using CRISPR/Cas9 gene editing methods (Gaj et al. 2013). Equally important is the fact that smaller rodents are "old" after 1 year (Ohlemiller et al. 2016), with a life expectancy typically less than 3 years. For all these reasons, studies of human presbycusis rely heavily on observations in aging animals, and especially rodents. The fundamental justification is that the same target cells are affected in animals and humans, with similar consequences for hearing. The presbycusis literature further supports overlapping genes and biochemical cascades for cellular injury in animals and humans (see Someya and Kim, Chap. 2).

3.3 Age-Related Perceptual Deficits: Cochlea or Brain?

In the same way that the retina builds a continuous picture of the world, the cochlea builds a continuous representation of the incoming sound spectrum using an array of sharply tuned frequency filters (Dallos et al. 2006). At each location on the basilar membrane, sharply tuned afferent neurons require sharply tuned inner hair cells (IHCs), and these in turn require sharply tuned outer hair cells (OHCs). OHCs, in turn, represent the substrate of the "cochlear amplifier," without which neither IHCs nor their afferent neurons will be sharply tuned. To survive and perform normally, both types of hair cells further require that a proper environment be established by

neighboring nonsensory cells, and that a large positive electrical potential exist in the endolymphatic fluid space above the organ of Corti. This potential, the endocochlear potential (EP), is generated by another epithelium, the stria vascularis. In this chapter these elements—hair cells, afferent neurons, and stria vascularis—will be the focus of how aging affects the cochlea.

The cochlea is a mechanical device whose cells sustain direct mechanical injury. However, noise damage to the cochlea can propagate in the auditory central nervous system (ACNS) at least to the auditory thalamus (Basta et al. 2005), and age-related changes can be identified at all levels up through auditory cortex (Caspary et al. 2008). ACNS changes due to noise or aging may include cell loss, demyelination, and synaptic modifications such as degraded temporal precision and altered excitatory and inhibitory balance (see Syka, Chap. 4; Recanzone, Chap. 5; Harris, Chap. 6). Aging is often associated with auditory perceptual deficits, some of which likely reflect cochlear pathology, and some that may not (e.g., temporally based tasks) (Ohlemiller and Frisina 2008). Since age-associated auditory perceptual deficits and ACNS pathology typically coincide with cochlear pathology that may—or may not—be detectable, some question has remained as to whether "central presbycusis" merely reflects cochlear changes (Humes et al. 2012). From the standpoint of molecular aging processes, however, both are inevitable and likely to proceed at least somewhat independently. Like cochlear sensory and supporting cells (Roberson and Rubel 1994), neurons in the brain are not replaced. This places a premium on their ability to maintain cellular homeostasis and carry out self-repair. These processes rely on intact nuclear and mitochondrial genomes, which are constantly under siege from radiation, carcinogens, and stochastic events (Evans et al. 1995; Someya and Prolla 2010). Recent discoveries in genetics have also highlighted the omnipresence of somatic (non-germline) mutations, during development and in adulthood (Evrony et al. 2015). In addition, the aging brain is subject to the influence of cerebrovascular disease and systemic conditions that may affect both the cochlea and ACNS in parallel. Finally, the conversation between cochlea and brain is not one-way. Inhibitory feedback from olivocochlear efferent neurons is likely altered by both cochlear and ACNS pathology (Kim et al. 2002). This could increase susceptibility to noise and decrease performance in noisy environments.

3.4 The Nature of Age-Related Cochlear Pathology

Most functional deficits of the aging cochlea are attributable to the loss or dysfunction of key cell types that are not replaced. Theories about aging processes distinguish between tissues that renew by mitosis and those that do not. The limitations of aging may operate by different mechanisms under these two conditions. Lost hair cells, afferent neurons, strial cells, and central auditory neurons are gone forever. Such irreplaceable cells must "decide" not to die every day, a decision that likely weights DNA damage, mitochondrial function, ATP stores, and the probabilistic flip of a coin (Childs et al. 2014). Cell death that reflects these factors may occur at a

low rate, but the process inexorably flows one way. By contrast, fibrocytes of the spiral limbus and ligament exhibit some mitotic potential (Lang et al. 2003) although it is not clear how much benefit this provides, or why evolution did not see fit to extend this capability to hair cells or neurons. Even mitotically active cells and tissues may be limited by factors that constrain the number of divisions possible, such as telomere length (Blackburn et al. 2015). Cells undergoing mitosis, including stem cells that serve to renew tissues, are also subject to inherited mutations and cumulative somatic DNA mutations.

To an observer, cell death might appear random, yet rules may govern how epithelia degenerate. One principle seems to be spatial continuity. The ion-tight boundary between endolymphatic and perilymphatic spaces is essential to cochlear function, and cell loss along this boundary could be catastrophic. In aging cochleas one can find dying cells along the endolymph/perilymph boundary, including strial marginal cells, Reissner's membrane cells, and supporting cells in the organ of Corti, yet the loss of these seems choreographed to seal boundaries simultaneously (Ohlemiller et al. 2018). This need not have been the case, and likely reflects selection pressure on the way epithelia respond to cell loss, whether from aging or other causes.

3.4.1 Classifying Presbycusis

There are many ways presbycusis might be divided into types, including the identity of the cells affected, causative processes, or causal genes. The genes and mutations that may drive presbycusis remain largely unknown (see Someya and Kim, Chap. 2). Kryter (1983) sought to separate aging effects into presbycusis ("pure" aging), sociocusis (noise-induced), and nosocusis (other injury), but these cannot be reliably distinguished. The most durable and influential scheme is one championed by Schuknecht (1964, 1993), based simply on noted cellular patterns of degeneration. Different patterns were suggested to correspond to particular shapes of the audiogram. The supposed link between the type of presbycusis and audiogram shape has both supporters (Vaden et al. 2017) and critics (Nelson and Hinojosa 2003; Allen and Eddins 2010), yet it remains one of the few noninvasive tools for inferring the nature of cochlear pathology.

The utility of Schuknecht's framework is that it is based on the type of cell(s) affected, which can ultimately be confirmed postmortem. The study of animal models also allows histopathological assessment, and this parallel approach in humans and animals has paid tremendous dividends. The patterns noted by Schuknecht are perhaps not particularly surprising, as they focus on major contributing cells and epithelia. One principle favored by Schuknecht is that the major contributing cell types—hair cells, neurons, and strial cells—can degenerate largely independently. This is an important point. Most cell types one might quantify will likely appear to decrease with age (Fig. 3.1), potentially obscuring causal relationships and giving rise to vague and unhelpful conceptions of presbycusis. But if there are distinct

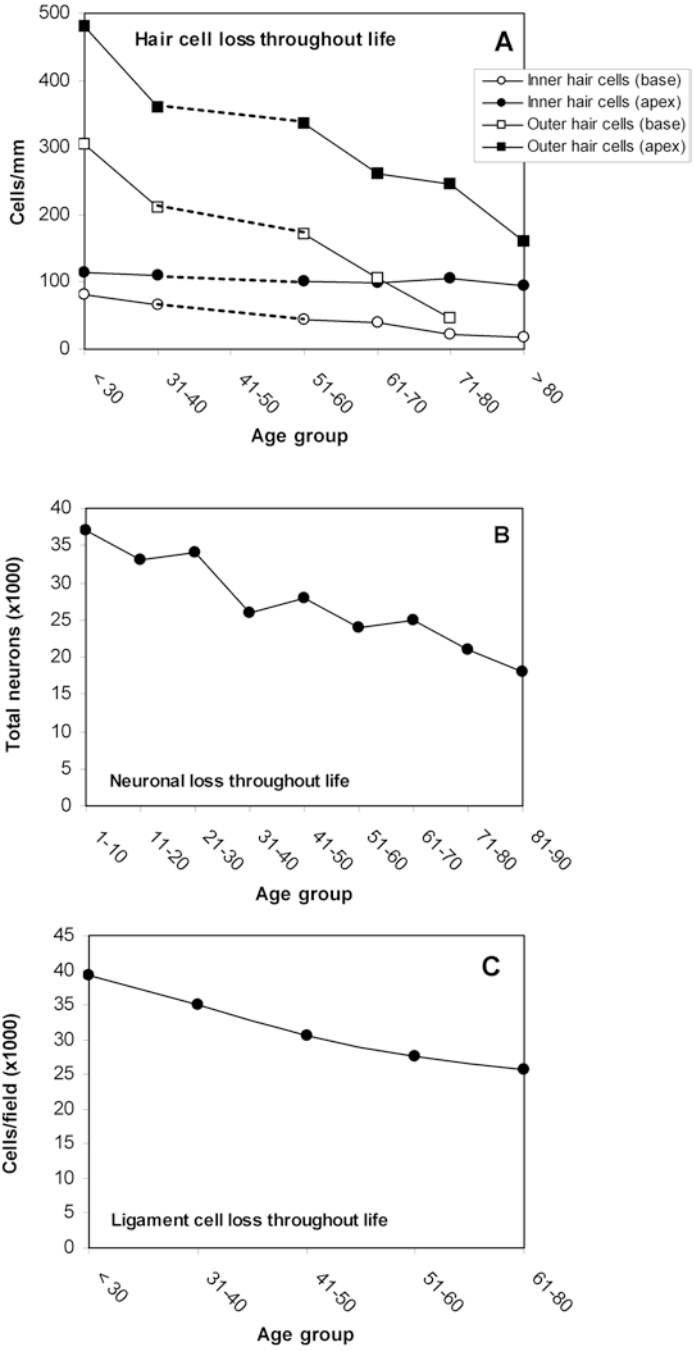

Fig. 3.1 Age-related sensory and nonsensory cell loss in human cochleae. (**a**) Inner and outer hair cell density versus age in the basal and mid-to-apical cochlea. Data were pooled across subjects of varying hearing ability. (Adapted from Bredberg 1968). (**b**) Total spiral ganglion cells versus age. (Adapted from Otte et al. 1978). (**c**) Density of fibrocytes in the cochlear spiral ligament versus age. Subjects had no known hearing impairment. (Adapted from Wright and Schuknecht 1972). (Reprinted with permission from Ohlemiller and Frisina 2008)

patterns of cell loss, and these patterns appear only in some people and some animal models, then there are "rules" to be discovered about gene–environment interactions and interdependencies among specific cell types. While it is probably true that the majority of human and animal temporal bones will show a mix of presbycusis types (Schuknecht and Gacek 1993; Nelson and Hinojosa 2003), underlying patterns can be dissected by comparing clinical cases and a broad variety of animal models. There are, to be sure, limits to the independence of various cell types: IHC loss can be expected to lead to eventual neural loss (Felder et al. 1997) and some forms of strial dysfunction can promote hair cell loss (Liu et al. 2016). But the clear existence of divergent cellular patterns and degrees of severity justifies the search for multiple, distinct, and discoverable causes.

3.4.1.1 Hair Cells and Organ of Corti

Organ of Corti pathology forms the basis of Schuknecht's "sensory" presbycusis, estimated to encompass 10% of presbycusis cases. As no primary age-related pathologies of supporting cells have been documented, sensory presbycusis practically collapses to inner and OHC loss, primarily the latter (Fig. 3.1). The process of transduction inexorably exposes inner and OHCs to mechanical stress. This is particularly true of OHCs, by virtue of their location at the radial point of maximal basilar membrane motion and the insertion of their stereocilia into the tectorial membrane (e.g., Liberman and Beil 1979). Basal OHCs may also be inherently more vulnerable to insults than are apical OHCs (Sha et al. 2001). OHCs are the primary target of most insults (noise, ototoxins, engineered mutations) one may impose in the laboratory. Depending on species, damaged OHCs may die, or simply fail to repair their soma or hair bundle. These statements are not meant to equate noise or ototoxic injury with aging. It may be that cumulative "microinjury" from otherwise nondamaging events is amplified by particular alleles, such as the *Cdh23*^{Ahl} allele or defective alleles encoding protective factors (Ohlemiller 2006), and OHCs represent the most vulnerable functional link in the chain.

Based on trends in animal models, OHCs appear to be the primary casualty of aging, seemingly contradicting Schuknecht's rather low estimate of the incidence of sensory presbycusis. After mice and gerbils, the remaining best-studied aging animal models also most closely model sensory presbycusis. These include guinea pigs (Covell and Rogers 1957; Coleman 1976), chinchillas (Bohne et al. 1990; McFadden et al. 1997), and rats (Chen et al. 2009). Although the prevalence of particular pathology in animals tells us nothing about prevalence of types of presbycusis in humans, a seismic shift may be underway based on recent reanalyses of some of the same specimens examined by Schuknecht. Wu and colleagues (Wu et al. 2020) reexamined archival celloidin-embedded human temporal bones using newer methods and have suggested that hair cell loss was underdiagnosed in the majority of cases. Thus, hair cell loss and sensory presbycusis may in fact represent the major form of age-associated hearing pathology in humans, in keeping with majority of animal models.

The environment of OHCs depends on the mechanical and biochemical influence of several types of supporting cells in the organ of Corti. These cells, which include pillar, Deiters, Hensen, Boettcher, and Claudius, are not typically quantified in morphometric studies, nor are physiological methods available to assess their function directly. The full roles of these cells are not known, and there are no estimates of how many may be lost without compromising function. When vital commonly expressed elements (e.g., connexin 26) are absent from these cells, OHCs may degenerate (Cohen-Salmon et al. 2002). Connexins form gap junctions that connect supporting cells electrotonically, and also form membrane channels for release of Ca^{2+} and ATP, which may help OHCs survive stress (Gale et al. 2004; Piazza et al. 2007). Thus, in some cases age-related OHC pathology may reflect loss of homeostatic support functions of neighboring cells in the organ of Corti.

3.4.1.2 Afferent Neurons

About 95% of cochlear afferent neurons are radial afferents that form synapses with IHCs (Spoendlin 1978). Each IHC may contact about 20 neurons (Liberman 1980). While the majority of afferent neurons have low thresholds and limited dynamic range (Liberman 1978), about 20% show high thresholds and "sloping saturation," and are suggested to extend dynamic range at any frequency (Sachs and Abbas 1974). These neurons, which typically show spontaneous firing rates (SRs) of 0–2 sp/sec, project to the small cell cap region of the cochlear nucleus, which in turn projects exclusively to nuclei that control cochlear efferent neurons (Ryugo 2008). Thus it has been proposed that low-SR/high-threshold neurons do not directly mediate perception of mid- and high-level sounds, but rather engage efferent responses that shift the dynamic range of the remaining neurons to higher sound levels (Carney 2018).

Loss of afferent neurons forms the basis of Schuknecht's "neural" presbycusis (Pauler et al. 1986; Schuknecht and Gacek 1993), estimated at 15%–30% of presbycusis cases. Schuknecht noted that some patients with clinically normal audiograms reported problems decoding speech in noisy settings and scored poorly on speech identification tests. Temporal bones from affected individuals showed at least 50% afferent neuronal loss (as measured by the density of cell bodies in Rosenthal's canal) with (reportedly) minimal hair cell loss. Based on these observations, Schuknecht defined neural presbycusis as a combination of normal thresholds, suprathreshold perceptual deficits, and at least 50% loss of afferent neuronal cell bodies. Human temporal bone studies show a pattern of neuronal loss over a typical life span (e.g., Makary et al. 2011) (Fig. 3.1), although only some cases reach 50% loss, suggesting a role for genetic and environmental factors. Animal models also support the general progressive loss of cochlear afferents with age (Gleich et al. 2016; Möhrle et al. 2016). It is likely that particular gene alleles act in concert with other factors to render some humans and animals more affected. However, no "proneural presbycusis genes" have been identified.

Both IHCs and their supporting cells may sustain afferent connections through the release of trophic factors (Sugawara et al. 2005). Loss of these factors, or perhaps excitotoxicity from overly active synapses, could disrupt this relation, leading to loss of neurons from normal-appearing IHCs (Moser and Starr 2016). When neurons are lost, or respond abnormally, it can be difficult to separate IHC pathology from neural pathology. The cochlear summating potential (SP), which can be recorded from the middle ear, eardrum, or using surface electrodes (Ferraro and Durrant 2006), is thought to reflect the responses of IHCs. Attempts to use the SP to separate IHC from neural injury have involved normalizing other responses (like ABR wave I or compound action potential N_1) to SP magnitude (e.g., Stamper and Johnson 2015). However, both the SP and wave I magnitude are highly variable, particularly in humans and larger animals, and there are no clear criteria for normal SP threshold or amplitude. As there exist few means to monitor IHC health, the contribution of IHC pathology to neural dysfunction can rarely be known.

Up until recently, isolated cochlear afferent neuronal loss appeared to be a common feature of aging with few known environmental causes. No manipulation was known to produce a "pure" neural lesion without hair cell pathology. This picture was challenged in a series of papers by Kujawa and Liberman (Kujawa and Liberman 2006, 2009), who exposed CBA/CaJ mice to modest noise that imparted only a temporary threshold shift (TTS). These mice evidenced little hair cell loss but showed loss of synapses and withdrawal of afferent dendrites from under IHCs. Eventually, up to half of afferent neurons died in these mice, despite the absence of detected hair cell pathology or permanent threshold shifts. Thus was born the notion of noise-induced cochlear synaptopathy and the idea that even a single exposure to modest noise could set up a lifelong trajectory leading to a diagnosis of neural presbycusis. This idea fits well with the frequently perceived loss of signal in noise during aging: Perhaps nearly everyone in most industrialized societies experiences enough noise to impart neural presbycusis. Additional studies suggested that the neurons most sensitive to damage are low-SR/high-threshold neurons (Furman et al. 2013). This would not affect ABR thresholds or audiograms but would be expected to produce suprathreshold hearing deficits. The mouse data also suggest that early synaptopathic noise exposures do not merely accelerate typical age-related changes but produce an unstable lesion that magnifies age-related neural losses (Fernandez et al. 2015).

Work in other animal models (chinchillas, rats, guinea pigs, rhesus monkeys) has shown synaptopathy to be a general effect of noise exposure (e.g., Möhrle et al. 2016; Hickman et al. 2018), although not always clearly in the context of TTS exposures (Valero et al. 2017). The severity of acute synaptic loss and the extent of repair vary by model. Complicating such comparisons is the fact that the time between synaptic or dendritic loss and loss of neural somata varies by species, so that it matters what is counted. Smaller mammals show more rapid loss of afferent cell bodies after losing their connections to IHCs than do larger animals or humans (Sergeyenko et al. 2013), and human temporal bones showing less than 50% neural soma loss (Schuknecht's criterion) often show more extensive loss of dendrites or synapses (Wu et al. 2020). Among inbred mouse models, similar synaptopathic effects have

been found in CBA/CaJ and FVB/nJ, while C57BL/6 J mice show substantial synapse repair (Shi et al. 2015; Song et al. 2016). Human temporal bone studies have not demonstrated a relation between noise exposure and neural loss (Makary et al. 2011; Viana et al. 2015). Moreover, to date combined physiological and psychoacoustic studies in humans have failed to produce consensus regarding any relation between noise exposure history and neural loss (Plack et al. 2014; Guest et al. 2017). Retrospective noise exposure assessments (typically self-reported) are not sufficiently accurate, and physiologic metrics for neural loss have not worked well. The latter have attempted to utilize the magnitude of ABR wave I elicited by loud sounds (Stamper and Johnson 2015) or the magnitude of steady-state responses to amplitude-modulated tones (Bharadwaj et al. 2014, 2015) as a proxy for the number of surviving neurons. These measures are highly variable and can be influenced by sex. Attempts to normalize wave I by later ABR waves (e.g., wave V), or using the SP, have not resolved these problems.

Human and animal afferent neural anatomy differ in a number of respects (Tylstedt et al. 1997; Glueckert et al. 2005), including a lack of myelination of neural somata and suggested ephaptic connections between neurons in humans. The authors of these studies suggest that aggregation of neural somata within human Rosenthal's canal electrically connects normal neurons with deafferented neurons, potentially preserving their activity and survival. Such features may render human afferent neurons—or at least their somata—especially resilient. Similar neural aggregates have been observed in the cochlear apex of old C57BL/6 mice (Fig. 3.2d) (Cohen et al. 1990), and in *Ly5.1* KO mice (Jyothi et al. 2010), potentially creating an opportunity to study them. Small animal models, particularly most mouse models, appear far more vulnerable to noise than are larger animals or humans (Saunders and Tilney 1980). From this, some aspects of noise-induced cochlear injury in animals may not translate to humans, nor can animals be used to establish safe exposure standards for humans. Of course, synaptopathy could accompany more severe lesions that include hair cell loss, but then suprathreshold problems might be dwarfed by threshold and tuning issues.

3.4.1.3 Cochlear Lateral Wall

The term lateral wall encompasses the stria vascularis and several fibrocyte types of the spiral ligament. Normal cochlear function requires that endolymph possess the character of an intracellular fluid—high K^+ and low Na^+ (Wangemann 2006). This composition of endolymph renders K^+ the major current carrier in cochlear transduction and places a premium on homeostatic mechanisms for regulating K^+ and Na^+, as well as Ca^{2+}. One suspected function of the architecture of both the organ of Corti and spiral ligament is to "recycle" K^+ from hair cells back to the stria vascularis, and ultimately back to scala media via a syncytium made of supporting cells of the lateral organ of Corti and spiral ligament fibrocytes (Weber et al. 2001). Like supporting cells of the organ of Corti, fibrocytes of the spiral ligament express connexins to form a nearly continuous network from the organ of Corti to the stria.

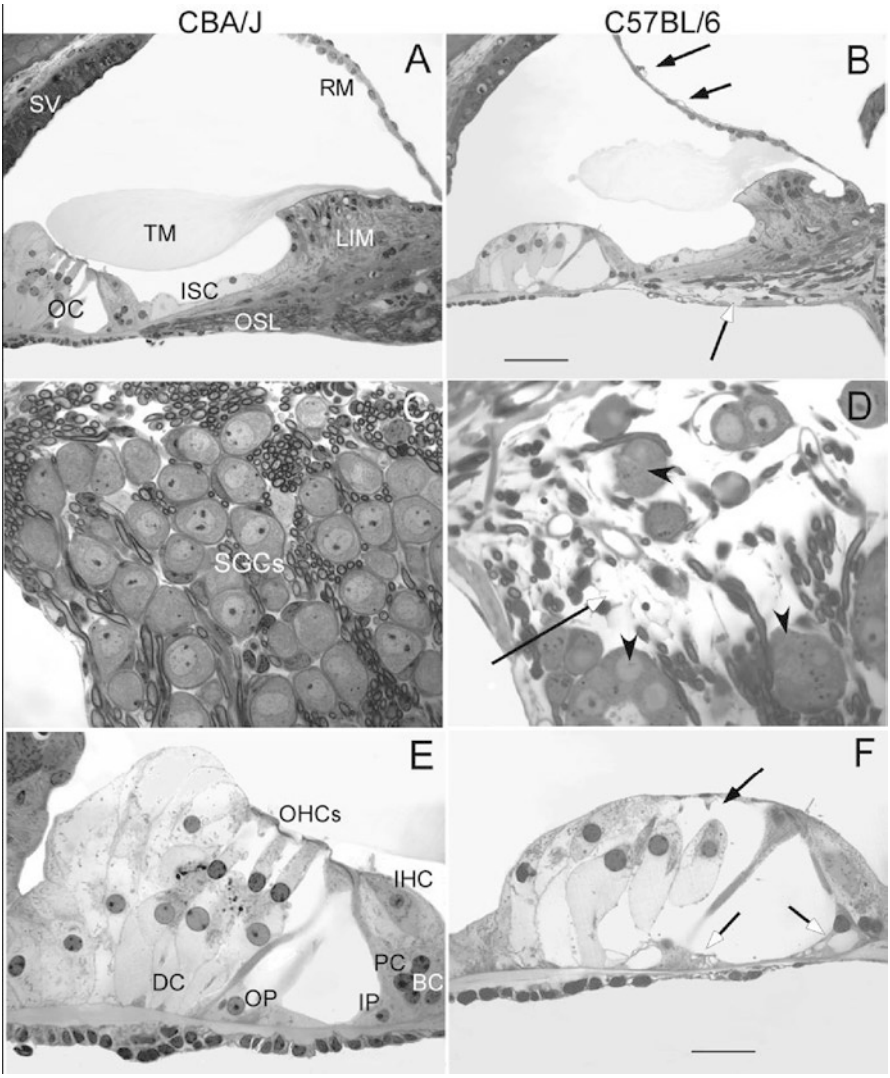

Fig. 3.2 Comparison of general features of the upper cochlear apex in an old CBA/J mouse (23 months) (**a**, **c**, **e**), and C57BL/6J mouse (20 months) (**b**, **d**, **f**). The CBA/J mouse shows few effects of aging. Pathology in the C57BL/6J mouse includes loss of neurons (**d**, plus white arrow in **b**), aggregation of neuronal cell bodies (black arrowheads in **d**), vacuolated mesothelial cells of Reissner's membrane (black arrows in **b**), loss of outer hair cells (black arrow in **f**), and vacuolated pillar cells (white arrows in **f**). BC border cell, DC Deiters cells, IHC inner hair cell, IP inner pillar cell, LIM spiral limbus, OC organ of Corti, OHC outer hair cells, OP outer pillar cell, OSL osseous spiral lamina, PC phalangeal cell, RM Reissner membrane, SGC spiral ganglion cells, SV stria vascularis, TM tectorial membrane. Scale bars: **a**, **b**, 50 μm; **c–f**, 20 μm. (Reprinted with permission from Ohlemiller and Gagnon 2004a)

This architecture makes optimal use of K^+ and avoids posited toxic effects of K^+ buildup around hair cells (Bohne 1972). This cellular network may also run in reverse, channeling glucose and other nutrients from strial capillaries back to the organ of Corti (Chang et al. 2008). Cells of the lateral organ of Corti and inferior spiral ligament also express connexin hemijunctions. These serve the release of Ca^{2+}, adenosine derivatives, and other factors that may promote the survival of hair cells (Gale et al. 2004).

The major supplier of K^+ to the stria is the spiral ligament. For this reason, pathology that is restricted to the ligament may still cause depression of the EP, even with a normal-appearing stria. This interdependency can blur the distinction between strial and sensory presbycusis (see Sect. 3.4.1.4). In terms of degeneration, dysfunction within spiral ligament typically exerts its most dramatic effects on the organ of Corti. A number of manipulations (noise, ototoxins, aging) can alter the appearance of the spiral ligament (Liang et al. 2005; Spicer and Schulte 2002), while the EP may be temporarily affected or unaffected (Ohlemiller et al. 2006). The most common ligament pathology affects type IV fibrocytes, which lie immediately adjacent to the organ of Corti (Hequembourg and Liberman 2001), and whose specific role has been difficult to demonstrate (Adams 2009). A cellular communication network may also function to protect IHCs and medial organ of Corti (Spicer and Schulte 1998; Spicer et al. 1999), although less is known about potential problems if this network is disrupted. One prominent structure in this medial loop is the spiral limbus, which often appears abnormal in old human and animal cochleas (Ohlemiller and Gagnon 2004a). Finally, loss of root cells from inferior ligament has been uniquely noted in old CBA/CaJ mice (Ohlemiller et al. 2010) (Fig. 3.3) and may help explain age-related EP reduction in these mice. Root cells may normally absorb K^+ to shunt current away from hair cells (Marcus and Chiba 1999). In CBA/CaJs, these are replaced with voids that appear open to the endolymphatic space, which could promote uncontrolled mixing of endolymph and perilymph that would "short out" the EP.

Fibrocytes of the spiral ligament and limbus are difficult to differentiate without cellular markers or EM analysis (Spicer et al. 1996), making detailed characterizations of ligament pathology impossible with standard light microscopy. Noting that temporal bone specimens often showed loss of fibrocytes in the spiral ligament, Schuknecht coined termed "conductive" presbycusis to cover this potential form. While many instances of age-related degeneration in the spiral ligament have been noted, the relation of these to hearing loss remains vague, and it may be difficult to separate some primary ligament dysfunction from either sensory or strial presbycusis (Sect. 3.4.1.4).

3.4.1.4 Stria Vascularis and the Endocochlear Potential

The endocochlear potential provides part of the electromotive force that drives K^+ through hair cells. Although the EP has been measured only anecdotally in humans (Tran Ba Huy et al. 1989; Kobayashi et al. 1996), strial thickness and volume have

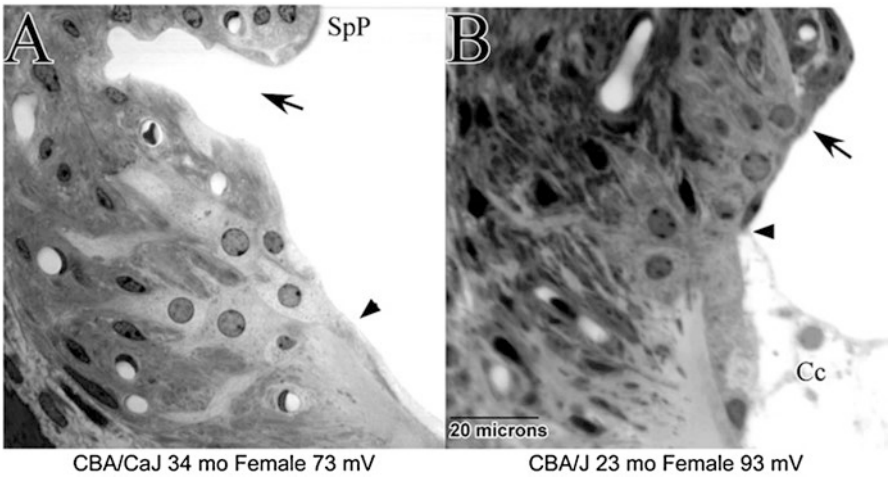

Fig. 3.3 Example lateral wall of the cochlear upper basal turn in an old CBA/CaJ female mouse (**a**) and an old CBA/J female (**b**). Age and endocochlear potential in each mouse are shown. The two images have been aligned to emphasize difference in survival of outer sulcus cells (OSCs)/root cells in the region just below the spiral prominence (compare locations at large arrows). Potentially related was a difference in the extent of coverage of OSCs at this location by spiral prominence epithelial cells. In CBA/J mice, the cells of spiral prominence (SpP) more often contact Claudius cells (Cc) of the organ of Corti. Small arrowheads in each panel denote the apparent end of Claudius cell processes, leaving more OSCs exposed to endolymph in the CBA/CaJ. (Reprinted with permission from Ohlemiller and Gagnon 2004a)

served as useful proxy measures for strial function, and human and animal observations have led to the assertion that up to half of strial function may be lost without EP reduction (Pauler et al. 1988; Schulte and Schmiedt 1992). Schuknecht applied strial metrics to temporal bones to propose "strial" or "metabolic" presbycusis as a distinct form, estimated at 20%–35% of cases. He further suggested that a "flat" audiometric configuration could be diagnostic. Diagnosis of strial presbycusis by audiogram has since been applied to argue that (1) strial presbycusis is relatively common among cases of presbycusis; (2) it is most common in post-menopausal women; and (3) it appears to have a strong genetic component (Gates et al. 1999; Gates and Mills 2005). This is an amazing degree of inference, considering the indirect evidence, and nearly theoretical status of strial presbycusis owing to a lack of EP recordings in humans. The foregoing claims are, however, consistent with the puzzling presence of estrogen receptors throughout the cochlea (Stenberg et al. 1999), and the observation that compared to men, hearing in women appears preserved up to menopause, after which women catch up with men (Hederstierna et al. 2007).

The dependence of thresholds on the EP is expected to be higher at high frequencies and has been estimated at approximately 1.0 dB/mV, based on acute application of furosemide (Sewell 1984). The effects of long-term EP reduction can only be estimated by chronic application of furosemide (Lang et al. 2003), or in aged

animals that happen to have a low EP. In such cases, the dependence may be somewhat shallower (approx. 0.5 dB/mV), perhaps reflecting some type of adjustment of the cochlear amplifier to a permanently low EP (Ohlemiller 2009). Very little is currently known regarding how—or if—the cochlea sets the EP at a constant value, or instead, adjusts the sensitivity of the cochlear amplifier (Mills et al. 1993; Wang et al. 2018). Animal models of age-related EP reduction show threshold elevation that corresponds to the EP change, so that any mechanisms for adjustment must be limited. Other aspects of EP variation, potentially including diurnal cycles, have not been explored.

Given the tentative status of strial presbycusis, animal models are key to establishing and characterizing it. It bears emphasis that the only way to find useful animal models is often to blindly assess species and strains for which little is known. The first model, the Mongolian gerbil, took advantage of the popularity of gerbils for auditory nerve studies (e.g., Schmiedt 1989; Ohlemiller et al. 1991). In studies of aging gerbils, it was noted that the best predictor of thresholds in aging animals was not hair cell loss (Tarnowski et al. 1991), but rather strial degeneration and EP reduction, fortuitously making gerbils a model of this disease. Many gerbil studies followed (e.g., Gratton and Schulte 1995; Gratton et al. 1997), implicating loss of strial capillaries and Na^+/K^+ ATPase as potential causal events. Strial marginal cells were suggested to be the first cells affected (Spicer and Schulte 2005), recapitulating one of Schuknecht's key findings (Schuknecht et al. 1974). Studies of single cochlear neurons in aging gerbils (Schmiedt et al. 1996) suggest that, in addition to elevating thresholds, chronic reduction of the EP reduces the responsiveness of low-SR/high-threshold neurons.

Comparison of inbred mouse strains has proven a valuable way to dissect pathology possessing genetic underpinnings, including strial presbycusis (Ohlemiller et al. 2016). Aging C57BL/6 (B6) mice show OHC loss and broad loss of fibrocytes from spiral ligament (Hequembourg and Liberman 2001), but do not show EP reduction with age (Ohlemiller et al. 2006). BALB/cJ mice (BALB) begin life with about an approximately 10 mV lower EP than B6, and after about one year tend toward further EP reduction, although not in all animals, and mostly in females. Histological metrics focused on lateral wall of BALBs revealed a relation between the EP, strial marginal cell density, and spiral ligament thickness (Fig. 3.4). Affected animals also showed fewer, larger, strial capillaries, suggesting a compensatory mechanism and potential anatomic marker for strial dysfunction. The results in BALB mice fit with expectations from human studies, including an emphasis on marginal cell pathology, a predilection for females, and a genetic basis, since identically raised B6 mice do not show EP reduction. The lack of EP reduction in B6 mice out to at least two years challenges the notion that broad and severe cochlear degeneration will always include a component of EP reduction. The BALB results also counter the assertion that severe hair cell loss will preserve the EP by eliminating leakage conductances, rendering such models misleading. B6 and BALB mice should show similar EP resilience because both strains show similar loss of hair cells (Willott et al. 1998).

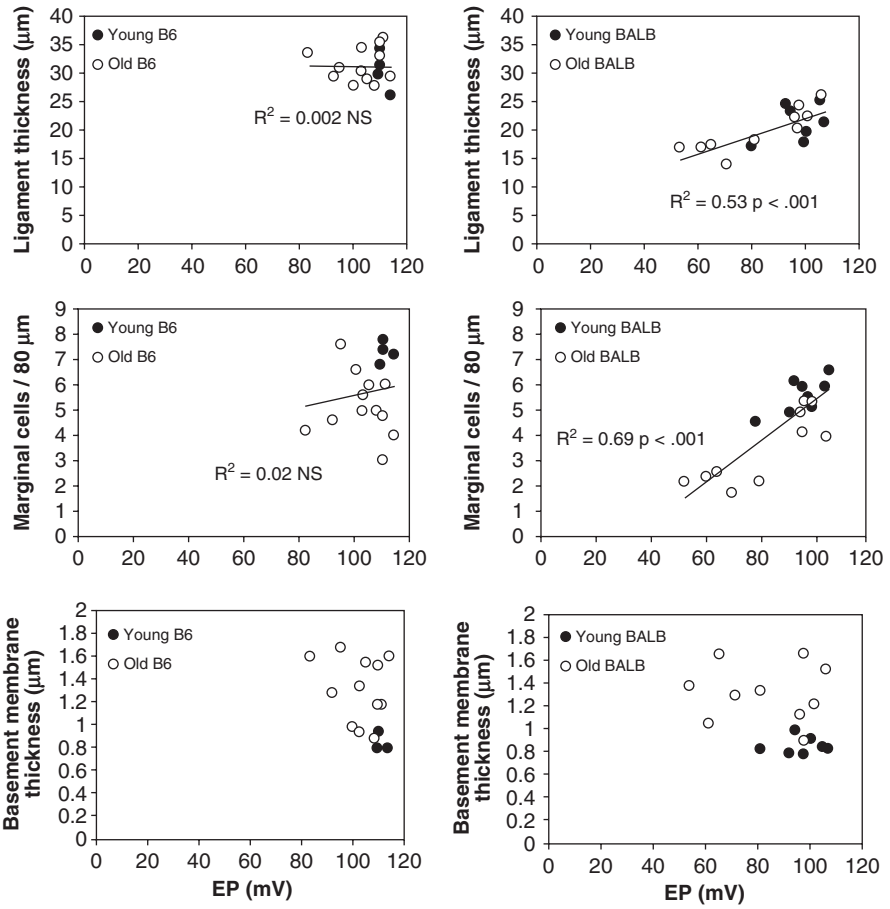

Fig. 3.4 Relation between basal cochlear turn endocochlear potential and spiral ligament thickness (top row), strial marginal cell density (middle row), and strial capillary basement membrane thickness (bottom row) in female C57BL/6 J and BALB/cJ mice. Each plot compares young (<3 months) and old (>19 months) within strain. Data for each animal are means from examination of upper basal turn in five sections. (Reprinted with permission from Ohlemiller 2006)

Further comparative studies revealed other useful models and tested the significance of melanin for protecting the stria. CBA/CaJ mice, the most popular "good hearing" strain for hearing research, show EP reduction after about one year (Ohlemiller et al. 2010). As in BALBs, the reduction appears more frequently in females and correlates with strial marginal cell loss. EP shifts in females appeared to accelerate after estropause, matching suggestions for human females and menopause. Not all animals showed age-related loss, again suggesting a role for environmental or stochastic events. Marginal cell loss was marked only by fewer nuclei, so that these cells appeared fewer and larger, without gaps between cells. Such marginal cell "thinning" has also been noted in some forms of genetic

pathology and has been found to coincide with reduced expression of several key marginal cell pumps and ion channels (Jabba et al. 2006). The role of melanin was tested in B6 congenic albino mice, which carry a naturally occurring null allele for tyrosinase (Ohlemiller et al. 2009). Unlike pigmented B6, these mice tend toward age-related EP reduction that again correlates with apparent marginal cell loss. At least in B6, marginal cells take up melanosomes from nearby strial intermediate cells, and over the life of the animal, visibly concentrate melanin (Fig. 3.5). Along with other evidence implicating melanin in protection from ototoxic strial injury (Conlee et al. 1986; Barrenäs and Holgers 2000), these observations support a role for melanin in preserving strial function with age.

From the preceding, inbred mouse strains with age-related EP reduction support claims from human and gerbil research. The real value of mouse models, however, is that they can be used both to characterize a disease and to map underlying genes. Unfortunately, it is not practical to map changes that may appear only in some old

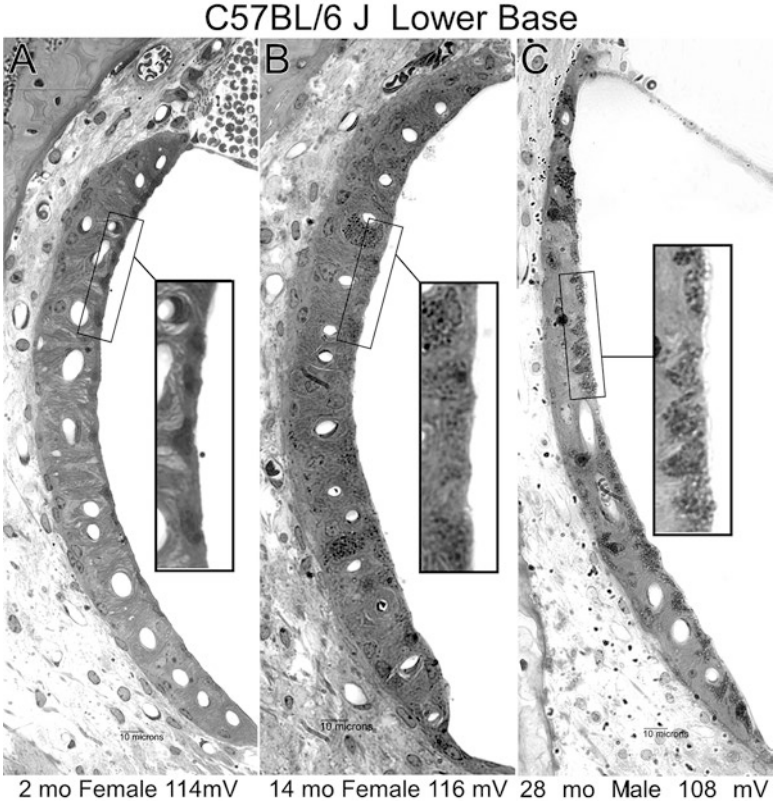

Fig. 3.5 Typical examples of stria vascularis in the lower cochlear base of old pigmented C57BL/6 J mice at three different ages, having normal endocochlear potentials. Young mouse (**a**) shows little pigment by light microscope. By 1 year (**b**), pigment can be seen in all strial layers. Late in life (**c**), pigment is especially concentrated in marginal cells. (Reprinted with permission from Ohlemiller et al. 2009)

animals, as is the case in BALB and CBA/CaJ mice. While a number of "pro-presbycusis" genes have been suggested (see Someya and Kim, Chap. 2), none clearly promote strial presbycusis. Although higher melanin content in the cochlea and skin have been associated with better hearing with age (Lin et al. 2012), this has not been linked to improved strial function, nor to evidence that melanin-related genes play a role. Notably, of a number of known, critical, molecular components in EP generation (e.g., Na^+/K^+ ATPase, NKCC1, Kir 4.1) (Nin et al. 2008) none of the underlying genes has been implicated in genome-wide association studies of presbycusis in humans or animals. Mice heterozygous for functional alleles encoding NKCC1 or either cochlear isoform of Na^+/K^+-ATPase showed progressive hearing loss and EP reduction, despite normal cochlear appearance (Diaz et al. 2007). In each case, however, homozygosity for the null allele was associated with elevated embryonic lethality. Presently, there is no evidence that noise sensitivity of the EP enhances the likelihood of strial presbycusis (Ohlemiller and Gagnon 2007), nor have any other insults have been shown to produce a strial presbycusis-like phenotype. If there are environmental risk factors for strial presbycusis, it remains unclear what these may be.

Animal models that reproduce key features of human strial presbycusis not only facilitate the study of this condition; their existence critically testifies to the *existence* of strial presbycusis. This is particularly true of the few "uncomplicated" models (gerbils, CBA/CaJ mice), where EP reduction accounts for most hearing loss. Of course, the *number* of emergent animal models of strial presbycusis tells us nothing about the prevalence of human cases, and it is difficult to evaluate claims that strial presbycusis is the dominant form of presbycusis (Schmiedt 2010). More animal models are needed, both to seek common elements and to identify risk genes. Gene mapping will remain a challenge, owing to the requirement to map a variable-penetrance trait using old animals. Identifying human cases also remains problematic if the audiogram is not diagnostically reliable. One proposed approach is to use the dynamic characteristics of DPOAEs to separate OHC dysfunction from EP reduction (Ueberfuhr et al. 2016). The EP is required for a functional cochlear amplifier and sensitive hearing, but it contributes little to OHC function at high sound levels. Accordingly, OHC pathology is expected to alter DPOAE input/output (I/O) characteristics at all sound levels, while a low EP is predicted to preserve DPOAE magnitude at high sound levels. That is, normal and "EP-compromised" DPOAEs should converge at high sound levels. This feature is easily confirmed in the laboratory, where experiments can be designed to compare DPOAE dynamics before and after imposed insults. It is less clear that it can work in the clinic where there are typically no "before" data. One variant on this approach is to compare ABR threshold shifts with DPOAE threshold shifts (Mills and Schmiedt 2004), based on expected normative values for each. A low EP will reduce receptor currents through both IHCs and OHCs. Because ABRs rely on both OHCs and IHCs, while DPOAEs assess only OHC motor responses, EP reduction is predicted to elevate ABR thresholds more than DPOAE thresholds, assuming the degree of elevation can be derived using normed values. To date, neither of these related methods has found wide support or use, likely because no specific treatment options exist for strial presbycusis versus other forms.

3.4.1.5 Other Nonsensory Cells

Beyond hair cells and neurons, the cochlea contains a host of specialized cell types, not all of whose functions are known. These cells have distinctive appearances and must express distinct sets of gene transcripts. Each cell type likely possesses a unique function, although little is known about how these cells may also share tasks. Based on a comparison of mice and marmoset monkeys (*Callithrix jacchus*), the distribution of cell "responsibilities" may also vary by species, as some key genes for cochlear function appear to be expressed in different cell types (Hosoya et al. 2016; Suzuki et al. 2016). Such dis-similar expression patterns may explain why some known deafness genes in humans do not cause deafness in mice. As most mammalian cochleas are composed of the same cell types, it is remarkable that some gene products and related functions can be divided up differently among cell types while preserving overall similarity of cochlear operation.

The appearance of the organ of Corti is subject to fixation artifacts so that it can be difficult to diagnose abnormal or missing supporting cells beyond Deiters or pillar cells. While some have attempted to capture subtle changes by measuring organ of Corti height, volume, etc. (e.g., Wang et al. 2002), only hair cells and neurons are routinely counted. If an entire cell type such as tectal cells, Hensen cells, or Boettcher cells (which appear only in the cochlear basal half) were absent, this might be easy to miss. While it is possible that some forms of presbycusis are caused by primary pathology of nonsensory cells, such cases may be lumped with sensory presbycusis due to hair cell loss or be classified as indeterminate if no cells are clearly missing. Figure 3.6 shows examples of dying supporting cells in the lateral organ of Corti of a 129S6/SvEv mouse (129S6) (Ohlemiller and Gagnon 2004b). This strain is used as a model of both "accelerated aging" and relative noise resistance (Yoshida et al. 2000). Such cell deaths do not clearly rearrange the organ of Corti, leave voids within the organ, nor openings in the reticular lamina. Pyknotic cells like those shown nearly always contact both the reticular lamina and Boettcher's cells. They were found to increase with age in BALB/cJ and CBA/J mice, but not 129S6 (Ohlemiller and Gagnon 2004b). Generally, the appearance of the organ varies considerably among models and studies while drawing little notice or comment. As an example, Figs. 3.2e, f compare the upper cochlear apex of old CBA/J and B6 mice. The B6 mouse shows loss of OHCs and neurons, as well as anomalies of pillar cells and Reissner's membrane. Nevertheless, the two organs show huge differences in conformation unrelated to pathology. These are not strain differences; rather, they are interanimal differences whose functional significance is unknown

3.5 Can Presbycusis Be Prevented by Preventing Injury?

Presbycusis and cochlear injury from other causes can be confoundingly similar, as demonstrated by the common features of old cochleas and injured cochleas. To separate these processes, one approach might be to study older subjects that have

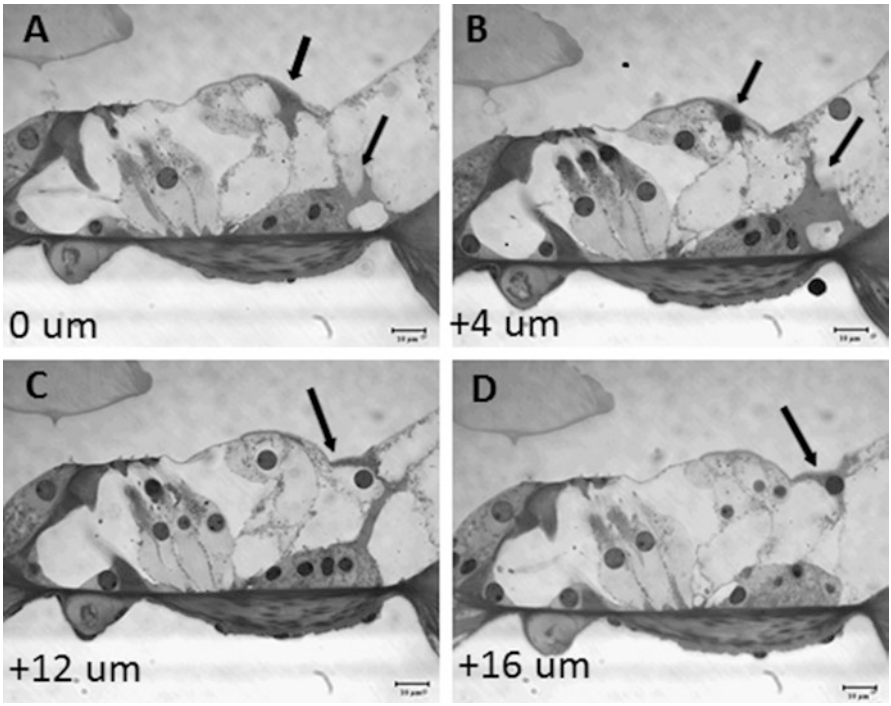

Fig. 3.6 (**a–d**) Partial section sequence through abnormal Hensen and Claudius cells (arrows) of the organ of Corti of the lower cochlear base of a 1.5-month-old 129S6/SvEvTac mouse. Normal complement of hair cells is present. Numbers in lower left of indicate distance through sectioned cochlea in microns. Two pyknotic cells (indicated by arrows) could be traced from the reticular lamina to contact with Boettcher's cells. Scale bar: 10 μm. (Adapted with permission from Ohlemiller and Gagnon 2004b)

been protected from insults. This is typically accomplished in human subjects by screening for noise exposure, or in animals by raising subjects in a low-noise environment.

3.5.1 Quiet-Aged Animals

All aging animal experiments require that injury be minimized. This optimally involves "quiet aging," whereby the animals are raised in a low-noise environment and all known ototoxins are eliminated. Aging Mongolian gerbils tend toward strial presbycusis, but also show other changes, even when quiet-raised. Disarray of IHC stereocilia—typically an aspect of noise injury—has been reported, as have missing and abnormally shaped OHCs (Adams and Schulte 1997). Altschuler et al. (2015) examined pathological changes in cochlear and neural status with age in UM-HET4 mice, a genetically heterogeneous population formed from four highly divergent

inbred strains lacking any known progressive hearing loss alleles. By 27–29 months of age, OHC loss was observed, mostly at the basal and apical ends. There was also an approximately 20%–34% reduction in afferent synapses by 22–24 months of age, despite minimal IHC loss. Differences in the onset of synapse and hair cell loss, and differences in the affected regions, suggest distinct mechanisms for hair cell versus synaptic pathology. These and similar examples indicate that preventing overt injury does not prevent hallmarks of presbycusis. Quiet-raised gerbils and UM-HET4 mice may carry alleles that magnify nonacoustic injury from processes like those described in Sect. 3.3.

3.5.2 Quiet-Aged Humans

Quiet-aging of humans cannot be experimentally controlled, but intriguing examples exist. Rosen et al. (1962) established contact with the Mabaans, an isolated tribe in the southeast Sudan. At that time, the Mabaans' daily lives lacked exposure to industrial-age noise. They were very fit and ate a frugal diet consisting mainly of ground millet, fish, nuts, and dates. They were also known for their keen sense of hearing. The Mabaans showed clinically normal hearing thresholds up to the eighth decade of life. Rosen (1966) later reported anecdotally that Mabaans who left the village to live in the city (Khartoum) began to show hearing loss.

The Mabaans' hearing ability declined with age, but they retained clinically normal audiometric thresholds. This best-known human example contradicts the animal results described in the preceding section. Like gerbils and UM-HET4 mice, Mabaans likely represent a genetically constrained population. Yet, unlike the animal models, Mabaans may carry few pro-presbycusis alleles, so that they show minimal hearing loss in the absence of real-world noise exposure. Such human–animal comparisons are not really equivalent because animal studies can be complemented by histopathology while the Mabaan studies could not.

3.6 Risk Factors for Presbycusis

Epidemiological analyses of human population-based data, including the National Health and Nutrition Examination Survey (NHANES), support a robust correlation between age and hearing loss. Fewer than 15% of adults aged 50–59 years have at least a mild hearing loss (>25 dB averaged across frequencies). By age 80, however, about 80% of people show at least a mild hearing loss. Still, the prevalence never reaches 100%, and these values greatly decrease with exclusion of mild audiometric hearing deficits (Goman and Lin 2016). While presbycusis remains highly prevalent, it is not inevitable and may be modifiable. The subsequent sections examine extrinsic and intrinsic risk factors. These further include modifiable and nonmodifiable factors.

3.6.1 Sex and Ethnicity

Human males often show more rapid onset of presbycusis than females, although this difference narrows once females reach menopause (Hederstierna et al. 2007, 2010). Sex would be generally considered a nonmodifiable intrinsic factor, although medical gender reassignment and use of hormone-based therapies could conceivably alter cochlear susceptibility. Differences in hormonal function (Frisina and Frisina 2013), participation in noisy activities (Marlenga et al. 2012), and poorer lifestyle choices among males (Spankovich and Le Prell 2014) may contribute to the influence of sex. Nevertheless, mouse data also support an effect of sex on both age- and noise-related hearing loss (Henry 2002; Milon et al. 2018).

Race/ethnicity represents another intriguing nonmodifiable intrinsic factor. African Americans have the lowest prevalence of hearing loss among all racial/ethnicity groups of older adults in the United States (Agrawal et al. 2008; Lin et al. 2011) despite the fact that they have statistically poorer access to health services, lower socioeconomic status, plus higher prevalence of diabetes, obesity, and other cardiometabolic factors (Bahrami et al. 2008; Chen et al. 2016). The explanation for this contradictory relationship is unclear, but likely involves a combination of extrinsic and intrinsic factors, including enhanced cochlear lateral wall resilience (Sun et al. 2014) and resistance to adverse health effects of cardiometabolic disease (Taylor et al. 2010a, b). Using data from the NHANES, Lin et al. (2012) examined the relationship between hearing level, race/ethnicity, and skin color, based on the Fitzpatrick skin type scale. This scale is a numerical classification of human skin color based on how skin responds to sun (i.e., always burns to never burns). The results indicated that skin color was a better predictor of hearing level than race/ethnicity. Sun et al. (2014) confirmed melanin pigmentation differences in African American versus Caucasian temporal bones. Notably, pigmentation was significantly higher in the stria vascularis and Rosenthal's canal of African Americans (see Sect. 3.4.1.4). This finding may also help explain the preservation of hearing in the Mabaan tribe, described by Rosen.

3.6.2 Lifestyle

Modifiable factors include noise exposure, ototoxic medications, socioeconomic status, health status, and lifestyle. Health factors shown to have relationships to hearing loss with age include diabetes (Fukushima et al. 2005; Bainbridge et al. 2008), cardiovascular health (heart disease, stroke) (Tan et al. 2018; Wattamwar et al. 2018), neurological health (Rosenhall et al. 2011), thyroid function (Moon et al. 2015), and immune health and autoimmune disease (Mancini et al. 2018).

Lifestyle factors including physical activity, dietary intake, and history of smoking have additionally been explored as modifiable factors for hearing dysfunction with age. These are also important for general health status but have direct and

indirect effects on hearing. Engdahl et al. (2015) examined the relationship between general health, disease, and lifestyle factors (not including dietary) and hearing loss. They found the effects of smoking, alcohol consumption, diabetes, weight, blood pressure, and physical activity were all significantly related to pure tone thresholds yet combined explained less than 0.5% of the variance. This finding at first glance appears to minimize the role of cardiovascular health and lifestyle in hearing loss. However, the analysis was limited by the cross-sectional nature of the data and the linear nature of the analysis, which did not consider odds of hearing loss based on common clinical and epidemiological definitions. Chapter 8 by Deal et al. provides a more comprehensive discussion of how some of these risk factors affect hearing.

3.6.3 Diet

In animal studies, dietary antioxidant supplements have reduced susceptibility to noise-induced hearing loss (e.g., Le Prell et al. 2011). However, in models of aging the relationship is less clear, with some studies showing protection (Le and Keithley 2007; Heman-Ackah et al. 2010) and others not (Sha et al. 2012). This may be due to genetic makeup of the animals tested, or the type, dose, or delivery method of the antioxidant supplement. In all such studies, the composition of the control diet is hugely important. If an animal is already consuming a diet containing adequate nutrition, the protective effect of nutrient loading may be limited. Such studies must also consider whether the species under test can synthesize a particular nutrient (McFadden et al. 2005).

In humans, meta-analyses of antioxidant supplements in prevention of age-associated disease show little benefit, and possible harm, in well-nourished populations (Bjelakovic et al. 2014). Similar findings have been reported for vitamin C supplements (Curhan et al. 2015). This does not mean that supplements cannot play a role in successful hearing with age. These agents may be more applicable to acute challenges (e.g., noise exposure), specific nutrient deficiencies, or particular genetic backgrounds.

Specific nutrients have been reported to reduce odds of hearing loss. These include B complex vitamins, plus vitamins A, C, E, and magnesium (for recent review see Spankovich 2015). Dietary patterns may also be important. These take into account food type (e.g., vegetarian) and quality. A series of studies on diet and hearing utilized the Healthy Eating Index (HEI), which measures how well a diet conforms to recommended guidelines of the U.S. Department of Agriculture (USDA). The HEI scores diets on a scale of 0–100, with 100 as the maximum "healthy" score indicating 100% of USDA recommendations. The score is a sum of subcomponents that examine variable aspects of diet. Some components provide higher scores with higher dietary intake (e.g., fruits), and others provide lower scores with higher dietary intake (e.g., sodium). The average HEI score for US adults is 64. Analyses using the NHANES dataset showed a significant relationship between HEI and hearing loss, where better diet was associated with better hearing and reduced report of tinnitus (Spankovich and Le Prell 2014; Spankovich et al. 2017). Specific

subcomponents showing relationships to better hearing included (1) diet variety, (2) higher intake of vegetables and fruits, and (3) lower intake of sodium and saturated fat. In addition, Curhan et al. (2018) examined the relation between Adherence to the Mediterranean Diet (AMED), Dietary Approaches to Stop Hypertension (DASH) recommendations, and the Alternative Healthy Eating Index-2010 (AHEI-2010, an updated version of the HEI). Participants with higher adherence scores for all three diets were associated with lower risk of hearing loss.

3.6.4 Genetics and Epigenetics

Presbycusis is a classic complex trait, with genetic and environmental roots. The heritability of presbycusis has been estimated at about 30%–50%, depending on age, study population, and how presbycusis is defined (Tu and Friedman 2018). The heritability of presbycusis is also likely to depend on the form. Since the major single indicator of hearing health is typically the audiogram, heritability studies probably inadvertently lump sensory and strial cases and miss cases of neural presbycusis, as the latter may not be reflected in threshold measures. Momi et al. (2015) examined the heritability of speech-in-noise (SIN) performance in 2076 twins. For subjects with normal thresholds, SIN scores would be expected to reflect neuronal survival and the extent of neural presbycusis, although this assumption has been questioned (Hoben et al. 2017). Age-adjusted heritability explained 25% of the SIN performance, whereas the remaining 75% was attributed to environmental factors unshared by the twins. Dietary factors were also identified as significant influences. From the Momi et al. study, the largest contributor to neural presbycusis appears not to be genetic.

Studies of genetic influences on disease typically distinguish between conditions that are inherited with high probability and little variation (Mendelian inheritance) versus highly variable conditions whose probability is a function of environment, plus alleles at multiple loci (Ohlemiller et al. 2016). To address the latter, genome-wide association studies (GWAS) are conducted. These studies identify statistical correlations between particular markers or alleles and disease probability in large populations. They can be performed in humans, and increasingly, in mice using newly developed panels such as the Hybrid Mouse Diversity Panel (Lavinsky et al. 2015), which incorporate a large amount of the genetic diversity across *Mus musculus*. While the primary phenotyping metric for most of these is the behavioral or ABR audiogram, other metrics may better capture particular pathologies. As gene sequencing becomes less expensive, brute sequencing—linking whole genome sequences with individual health metrics—is increasingly used to identify risk alleles and sequences (Lewis et al. 2018). The key in such studies is to correctly classify "normal" cases using the correct metrics. GWAS have identified presbycusis risk genes that impact protective/repair functions and inflammation, as well as other types of genes that may seem less intuitive (see Someya and Kim, Chap. 2). Potential risk genes include not only conventional protein-coding genes, but also regulatory RNA genes, which can effectively silence other genes (Hu et al. 2018).

The field is also at the beginning of a revolution over the realization that epigenetic modifications to DNA can set lifelong patterns of health and disease (Lacal and Ventura 2018). Epigenetics operate according to the nearly Lamarckian principle that our genes can be reprogrammed by what happens to us. Whole sets of genes can be silenced by methylation of key DNA base residues, creating functional knockouts for the affected genes. Such inactivation presumably evolved as an adaptive process, serving to turn off unneeded genes in development. However, its effects are far more wide-ranging, and it is difficult to see adaptive value in some of these. Perinatal and early life stress, including starvation of mother, baby, or even grandparents, appear to shift the baby's metabolism in ways that promote age-associated disease, potentially including presbycusis (Watanabe and Bloch 2013; Bouzid et al. 2018). This is an area ripe for new research, and where animal experiments should reveal important principles.

3.7 Summary

Presbycusis is a complex trait whose various forms reflect different mixes of genes, environment, and chance. The dominant framework for classifying presbycusis, advocated by H. Schuknecht, emphasizes injury to the organ of Corti (sensory presbycusis), afferent neurons (neural presbycusis), and stria vascularis (strial presbycusis). These are asserted to degenerate largely independently, reflecting separate environmental and genetic causes. Animal models reproduce most features of the human disease and collectively support a large hereditary component. Examination of multiple inbred strains of mice has facilitated the separation of cause and effect and led to the discovery of some genes and gene types. Most animal models show the hallmarks of sensory presbycusis (primary loss of hair cells), and recent reexamination of human temporal bones suggests this may represent the dominant form. A few animal models (gerbils, some mouse strains) resemble strial presbycusis. Among the features of this condition, primary marginal cell pathology, higher prevalence in postmenopausal females, and protection by cochlear melanin have been indicated by human studies and reproduced in animals. Among the posited forms of presbycusis, strial presbycusis may be the most strongly genetically influenced, as no environmental event has been shown to produce a strial phenotype. Pro-strial presbycusis genes remain elusive, however. The relation between strial and spiral ligament degeneration remains poorly understood, and presently it is not clear whether age-related spiral ligament degeneration more closely aligns with strial or sensory presbycusis.

Essentially all animal models and humans show loss of cochlear neurons with age, even where IHCs appear normal. This common loss may help explain the most frequent complaint of hearing in aging (poor speech understanding in noise) but may not always merit a label of neural presbycusis (>50% loss of neuronal somata and poor speech recognition scores). Animal studies indicate that the anatomic hallmarks of neural presbycusis can be produced by a single "synaptopathic" noise

exposure that does not impact thresholds or hair cell integrity, although the severity of the lesion and degree of synaptic repair vary with species. Noise as a cause of apparent neural presbycusis remains to be convincingly demonstrated in humans. The hereditary component of neural presbycusis may be small, and no pro-neural-presbycusis genes have been confirmed.

Attempts to minimize cochlear injury in humans and animals may slow presbycusis, but also reveal underlying genetic influences. The risk of presbycusis varies by sex, ethnicity, lifestyle choices (diet, exercise, smoking, alcohol consumption), and related health metrics (body mass, blood pressure, heart disease, thyroid function, diabetes, immune function). At least up to menopause, women fare better than men. This cannot solely reflect behaviors and may derive from a protective effect of estrogen. Highly melanized skin may be associated with resistance to presbycusis, perhaps because it coincides with increased cochlear strial melanin. As for all age-related diseases, the decades-long onset and heterogeneity of presbycusis have made it difficult to design effective therapies. Risk genes will likely be found to encompass a host of small-effect mutations that are not conducive to gene therapy. While certain dietary supplements (e.g., antioxidants, Ca^{2+} inhibitors, anti-inflammatories) and healthy living may slow presbycusis, the ultimate answer may be to unlock the genetic constraints to continual tissue renewal.

Compliance with Ethics Requirements Kevin Ohlemiller declares that he has no conflict of interest. Chris Spankovich declares that he has no conflict of interest.

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Chapter 4
Age-Related Changes in the Auditory Brainstem and Inferior Colliculus

Josef Syka

Abstract Aging is accompanied by specific changes in the processing of sound information that result from dysfunction of individual parts of the auditory system. Age-related changes in the function of the inner ear caused by pathologies occurring in the outer and inner hair cells (OHCs and IHCs), stria vascularis, and neurons of the spiral ganglion are transmitted to the central auditory system, where further pathological changes take place. The goal of this chapter is to describe aging-related changes that occur in the structure and function of the cochlear nuclei, nuclei of the superior olivary complex, and inferior colliculus. These changes inevitably influence the processing of acoustical information. Major pathological changes occurring in this part of the auditory system represent age-related losses of some specific types of neurons or their parts, particularly those connected with inhibitory functions. As a result of these losses, the processing of the fine temporal details of the acoustical signals appears to be impaired, particularly in the case of such complex signals as human speech. In addition, the brainstem and midbrain parts of the auditory system play important roles in the processing of space information and in the control of the intensity of the incoming acoustical signal by the olivocochlear bundle; both of these functions may be negatively influenced by aging. The effects of aging are described systematically as they appear in the structure, neurochemistry, and function of the brainstem and midbrain parts of the central auditory system.

Keywords Central auditory system · Cochlear nuclei · Efferent system · Inhibitory neurons · Neuronal loss · Olivocochlear bundle · Presbycusis · Space information · Speech in noise · Superior olivary complex · Temporal processing

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4.1 Introduction

It is well known that aging significantly influences the structural and functional properties of the cochlea (Ohlemiller and Spankovich, Chap. 3). Consequently, information that is transmitted from the cochlea to the central auditory system via the auditory nerve must be different in aged subjects when compared with young controls. In addition, the processes of aging impose deleterious effects on the central auditory system itself that further negatively influence information processing of the acoustical signals. It is the aim of this chapter to describe the state of knowledge regarding age-related changes in the processing of acoustical information in the lower parts of the central auditory system, including the cochlear nuclei, superior olivary complex (SOC; a full list of abbreviations used in this chapter is provided in Table 4.1), and inferior colliculus (IC). The age-related changes are described systematically as changes in the structure, neurochemistry, and function of the cochlear nuclei, SOC, and IC. As an important part of the brainstem auditory system represents an efferent olivocochlear bundle that controls the function of the cochlear hair cells, the age-related changes in this important descending pathway are also included.

4.2 Age-Related Changes in the Structure of the Cochlear Nucleus

Auditory nerve fibers, before reaching their targets in the cochlear nuclei, divide into an ascending branch that supplies the anteroventral cochlear nucleus (AVCN) and a descending branch that supplies the posteroventral cochlear nucleus (PVCN) and dorsal cochlear nucleus (DCN) (Cant 1992). All three subnuclei are tonotopically organized. Primary auditory fibers contact the spherical bushy cells and globular cells in the ventral cochlear nucleus (VCN) with large synapses called the bulbs of Held. Auditory nerve fibers also contact other cells present in the VCN, including octopus cells, multipolar cells, and small cells, making smaller synapses on these cells. The DCN represents a very complex neuronal structure, with auditory nerve fibers reaching pyramidal (fusiform) cells and giant cells. In addition to these excitatory neurons, several inhibitory interneurons, such as stellate cells, Golgi cells, and cartwheel cells, are involved in the processing of information in the DCN.

As it has been known for a long time that aging is associated with the loss of sensory hair cells and spiral ganglion neurons in the cochlea, one of the first questions asked by investigators was to what extent these losses are followed by neuronal losses in the auditory brainstem and midbrain. In one of the first papers describing age-related changes in the cochlear nucleus (CN; Feldman and Vaughan 1979) the authors noted that in very old Sprague–Dawley rats there was no evidence of cell loss in the CN when compared to young rats. However, this finding was not confirmed in further investigations.

Table 4.1 Abbreviations used in this chapter

ABR	Auditory brainstem response
AC	Auditory cortex
AMFR	Amplitude modulation following response
ASR	Acoustic startle reflex
AVCN	Anteroventral cochlear nucleus
CB	Calbindin
CB-ir	CB-immunoreactive
CBP	Ca^{2+}-binding protein
CF	Characteristic frequency
ChAT	Choline acetyltransferase
CIC	Central nucleus of the inferior colliculus
CN	Cochlear nucleus
CR	Calretinin
CS	Contralateral suppression
DCN	Dorsal cochlear nucleus
DIC	Dorsal cortex of the inferior colliculus;
DPOAE	Distortion product otoacoustic emission
EFR	Envelope-following response
EIC	External cortex of the inferior colliculus
FFR	Frequency following response
GABA	γ-Aminobutyric acid
GAD	Glutamic acid decarboxylase
GDT	Gap detection threshold
IC	Inferior colliculus
IHC	Inner hair cell
LFPS	Local field potentials
LOC	Lateral olivocochlear
LSO	Lateral superior olivary nucleus
MGB	Medial geniculate body
MGT	Minimal gap threshold
MLR	Middle latency response
MNTB	Medial nucleus of the trapezoid body
MOC	Medial olivocochlear
MSO	Medial superior olivary nucleus
NLL	Nucleus of the lateral lemniscus
OHC	Outer hair cell
PV	Parvalbumin
PVCN	Posteroventral cochlear nucleus
PV-ir	PV-immunoreactive
Pycs	Pyrroline-5-carboxylate synthetase enzyme
rBMF	Best modulation frequency for rate
SAM	Sinusoidally amplitude-modulated

(continued)

Table 4.1 continued

sBMF	Best modulation frequency for synchronization
SOC	Superior olivary complex
SPO	Superior paraolivary nucleus
tMTF	Temporal modulation transfer function
VC	Visual cortex
VCN	Ventral cochlear nucleus
VNTB	Ventral nucleus of the trapezoid body

The topic was studied by James Willott and his group (Willott et al. 1987), mostly in mice, using two mice models of age-related hearing loss. One of them was the C57BL/6J strain, which undergoes progressive sensorineural hearing loss with onset during young adulthood, and other one was the CBA/J strain, which displays only moderate hearing loss with onset late in life. In C57 mice the number of cells in the AVCN slightly decreased in the first year of life but remained stable later, despite chronic severe hearing impairment. In contrast to this, the CBA mice showed a reduction in AVCN cell number only during the second year of life. Morphological changes in the C57 mice occur mostly in the dorsal part of the AVCN that represents projection from the high-frequency part of the cochlea. This corresponds with the major loss of spiral ganglion cells in this mouse strain that is present in the base of the cochlea. Age-related morphological changes, such as loss of neurons and loss of primary dendrites, are also present in both C57 and CBA mouse strains in the octopus cell area in the PVCN (Willott and Bross 1990).

Evidently, the loss of auditory nerve fibers connected with aging (Ohlemiller and Spankovich, Chap. 3) may influence the state of synapses at the surface of the targeting cells in the CN. Endbulbs of Held, large axosomatic endings of myelinated auditory nerve fibers that target bushy cells in the AVCN, play an essential role in preserving timing information used for sound localization (Grothe et al. 2010) and spectral processing (Shofner 2008). The size of the synaptic area and synaptic complexity of endbulbs of Held were found to decrease with aging in CBA mice (Muniak et al. 2018). The gradual atrophy of endbulbs of Held was found to correlate with the reduction of auditory brainstem response (ABR) amplitude, both processes being faster than the relatively slow increase in hearing thresholds (Muniak et al. 2018). The reduction of ABR magnitude with age correlated in CBA mice closely with age-related loss of ribbon synapses of the IHCs that is followed with a delay of several months by a loss of auditory nerve fibers (Sergeyenko et al. 2013). These results indicate that central auditory pathologies may emerge as a consequence of the so-called "hidden hearing loss."

Similar age-related degenerative processes as in the AVCN also occur in the aging DCN in CBA and C57 mice (Willott et al. 1992). Naturally, the age-related changes are more expressed in the C57 mice, particularly in layer III, which is the layer receiving most of the DCN's primary auditory input. The volume of the DCN in C57 mice was found to decrease and the mean size of neurons as well as the number of neurons to decline, whereas these changes were found to be minimal, if

any, in CBA mice. Given the significant peripheral neurodegeneration in C57 mice, their DCN age-related changes may represent a case of induced changes and not central age-related changes per se (Willott et al. 1992).

Precise quantitative data on the age-related changes in the number of neurons in the PVCN and DCN in mice are available (Idrizbegovic et al. 2001, 2003). The authors used a quantitative stereological method, optical fractionator, to determine that aging in C57 mice is connected with a significant decrease in the number of neurons in both DCN and PVCN (Idrizbegovic et al. 2003), whereas in CBA mice a significant decrease occurs only in the DCN.

Several attempts to characterize structural changes in the human CN with aging have yielded inconclusive results. Königsmark and Murphy (1972) evaluated the volume and number of neurons in the VCN of postmortem patients and found an age-related increase in the volume, with, however, no significant changes in the number of neurons. In contrast, Arnesen (1982) described an essential decrease in the number of neurons in the VCN of humans diagnosed with presbycusis. Hinojosa and Nelson (2011) tried to quantitatively characterize the changes in the number of neurons with presbycusis in human cochlear nuclei. They analyzed the temporal bones and cochlear nuclei from six individuals with normal hearing and four individuals with presbycusis. Their presbycusis subjects exhibited a reduced spiral ganglion population. However, the mean CN neuron population was found to be significantly higher in the presbycusis group (around 114,000 neurons) than in the normal hearing group (around 91,000 neurons). The authors did not explain the reason for this unexpected finding, and therefore an explanation of this result awaits further study.

In summary, aging is connected with losses of neurons and changes in their size and dendritic tree in all subnuclei of the CN with differences present between animal species and even between animal strains. In addition to this, in consequence of the degeneration of spiral ganglion neurons, the number of incoming nerve fibers, along with their synapses on CN neurons, decrease. Synapses of targeting fibers, particularly endbulbs of Held, lose their complexity. These changes may also occur in human cochlear nuclei with aging however, the results of human studies are so far inconclusive.

4.3 Age-Related Changes in the Neurochemistry of the Cochlear Nucleus

It has been known since the publication of Banay-Schwartz et al. (1989) that the levels of glutamate and related amino acids in the CN are significantly affected by aging. Currently we know, on the basis of measurements with quantitative high-performance liquid chromatography, that the glutamate levels in Fischer 344 × Brown–Norway rats substantially decrease with aging in all subnuclei of the CN (Godfrey et al. 2017).

In contrast to this, aging does not strongly influence the levels of γ-aminobutyric acid (GABA) in the CN and similarly does not significantly change the enzymatic

activities connected with GABA (Raza et al. 1994). These authors measured the activity of enzymes in the CN of Fischer 344 rats, as well as in the nuclei of the lateral lemniscus (NLL) and in the IC. They found that aging did not alter the activity of the GABA synthesizing enzyme glutamic acid decarboxylase (GAD) in the CN, whereas GAD activity in the IC and NLL showed significant age-related decreases.

An important role in the CN is played by the inhibitory mediator glycine, with high levels of glycine being present in the cochlear nuclei and SOC, but not in the higher nuclei of the central auditory system (Godfrey et al. 2017). The results of several electrophysiological studies (e.g., Xie and Manis 2013) confirm that glycine is important for the function of cochlear nuclei. Glycine receptor binding sites are possible to localize using [^{3}H]strychnine binding. A significant decrease in [^{3}H] strychnine binding in the AVCN and DCN was found in 26-month-old rats in comparison with 3-month-old rats (Milbrandt and Caspary 1995). Similar age-related changes were observed in rats in mRNAs for the α_1, α_2, and β subunits of the glycine receptor (Krenning et al. 1998). When compared with the 3-month-old rats, the expression of mRNAs for α_1 and β subunits in the AVCN decreased in old-age groups, while the expression of mRNA for the α_2 subunit increased. Further details on age-related changes in glycine receptors were provided by Wang et al. (2009), who concentrated on fusiform cells in the DCN of rats. The age-related increases in hearing thresholds and in gap detection thresholds were accompanied in DCN fusiform cells by increases in the α_1 subunit message and with decreases in the α_1 protein. In support of the age-related decrease of α_1 protein levels in the DCN, there was a significant age-related decrease in the total number of glycine receptor binding sites with no significant change in affinity. The authors hypothesized that the described age-related changes in the fusiform cells of the DCN may contribute to the deterioration of temporal coding that accompanies presbycusis.

A similar age-related decrease in the number of strychnine-sensitive glycine receptors found in the DCN of F344 rats was also observed in C57 mice, whereas old CBA mice did not demonstrate such changes (Willott et al. 1997). For other neurotransmitters, age-related changes were reported concerning acetylcholine. When the activity of choline acetyltransferase (ChAT) was compared in the CN, NLL, and in the central nucleus of the inferior colliculus (CIC), the highest activity was found in the CN. It did not, however, change significantly with aging; significant age-related changes were found only in the CIC (Raza et al. 1994).

Evidence has accumulated that small age-dependent changes in Ca^{2+} regulation might gradually modulate normal brain aging and, in turn, increase vulnerability to neurodegenerative diseases (Toescu et al. 2004). Several small cytosolic Ca^{2+}-binding proteins (CBPs)—parvalbumin, calbindin, and calretinin—are important in Ca^{2+} buffering. The role that they play in the aging of the CN was studied by the Canlon group. They determined the total number of neurons immunostained with parvalbumin, calbindin, and calretinin in the DCN and PVCN of several mice species during aging. In CBA/CaJ mice (Idrizbegovic et al. 2001), aging was accompanied in the DCN by an increase in the representation of parvalbumin-immunopositive neurons and calbindin-immunopositive neurons. In the PVCN, only the number of parvalbumin-immunopositive neurons increased, whereas calretinin-immunopositive neurons did not change their representation with aging either in the

DCN or PVCN. As reported in Sect. 4.1, the total number of neurons in the CN of the CBA mice decreased with aging in the DCN and did not change in the PVCN.

In the fast aging mice strain C57, the CBP changes in the CN induced by aging were comparable with the changes of peripheral pathology (spiral ganglion loss, IHC and OHC loss). Specifically, a correlation between the increased numbers of the parvalbumin-immunopositive neurons in the DCN and PVCN and the degree of peripheral pathology was found (Idrizbegovic et al. 2003). A positive correlation was also present in the PVCN between the age-related increase of the calretinin-immunopositive neurons and the degree of peripheral loss of neurons and hair cells. The correlation between the increase in the number of CBP-immunopositive neurons in the CN with the loss of peripheral hair cells and neurons represents, according to the authors of the study, an attempt of the central auditory system to compensate for the diminished input from the cochlea.

The BALB/c mouse is an established model for the early development of sensorineural hearing loss. By 24 months of age this strain has an almost complete loss of OHCs, the IHC loss is almost complete in the apical and basal part of the cochlea, and a corresponding loss occurs in spiral ganglion neurons (Idrizbegovic et al. 2006). The total number of neurons in the DCN and PVCN decreases due to aging by 25%, while the proportion of parvalbumin-immunopositive and calretinin-immunopositive neurons in the DCN and PVCN significantly increases in comparison with the number of all Nissl stained neurons (Fig. 4.1). In BALB/c mice a similar

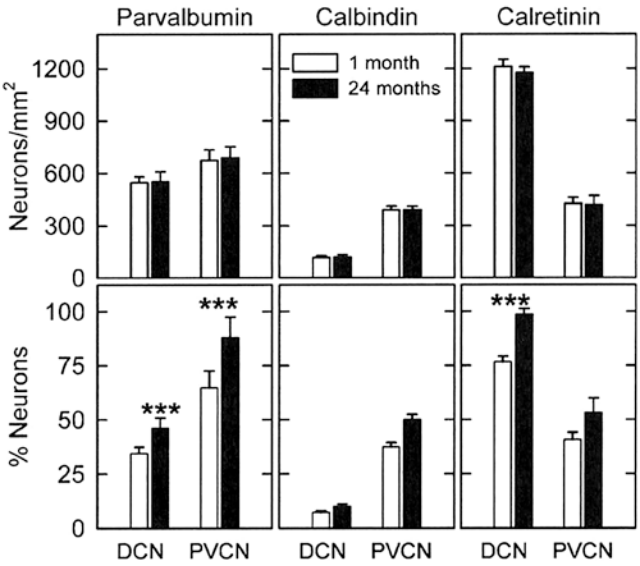

Fig. 4.1 Quantification of the density of immunopositive neurons in the dorsal cochlear nucleus (DCN) and posteroventral cochlear nucleus (PVCN) for parvalbumin, calbindin, and calretinin of 1- (open bars) and 24- (closed bars) month-old BALB/c mice (upper part). Percent of Nissl stained neurons that are immunopositive for parvalbumin, calbindin, and calretinin in the DCN and PVCN of BALB/c mice (lower part). The asterisks indicate statistical differences (***$p < 0.001$). (From Idrizbegovic et al. 2006)

positive correlation was found between the occurrence of CBP-immunostained neurons in the CN and the degree of the peripheral pathology as in C57 mice. Overall, in the BALB/c and C57 mice a large loss of peripheral receptors occurs, accompanied by a decrease in the total number of neurons in the PVCN and DCN; however, this loss is compensated by an increase of some CBP-immunostained neurons. As found in many other regions of the central nervous system, increased calcium–binding protein immunoreactivity compensates for the increased intracellular calcium concentrations occurring in neurons during aging (Verkhratsky and Toescu 1998).

Several other age-related changes were observed in the neurochemistry of the CN in experimental animals. For example, a loss of BDNF proteins was observed in the central processes of spiral ganglion neurons in rats and gerbils (Rüttiger et al. 2007). The authors believe that reduced BDNF protein levels in the auditory nerves with age may be a crucial factor in the altered brainstem plasticity observed during presbycusis. Mitochondrial dysfunction may also be implicated in the process of aging of the auditory function. This idea was supported by experiments with mtDNA mutator mice with increased levels of somatic mtDNA mutations (Niu et al. 2007). The animals displayed progressive apoptotic cell loss in the spiral ganglion and increased pathology with increasing age in the stria vascularis. The neurons in the CN showed an accelerated progressive degeneration with increasing age compared to the wild-type mice. Aside from this mouse mutant, named the Polg knockin mouse (Trifunovic et al. 2004), several other mouse models of age-related mitochondrial neurosensory hearing loss exist: MCAT transgenic mice, *Gpx1*KO mice, *Bak* KO mice, and *BCL2* transgenic mice, as reviewed by Han and Someya (2013) and in Someya and Kim, Chap. 2.

In summary, aging is accompanied in the CN by decreases in the activity of main neurotransmitters (glutamate and glycine). Several studies confirm an age-related decrease in the glycine receptors both in rats and mice. The age-related changes of calcium-binding proteins in the CN usually move in the opposite way, increasing with aging. The CBP age-related changes in the CN are area specific and also strain specific, and the increase with aging is more expressed in the C57 mice than in CBA mice. An increase of parvalbumin- and calbindin-immunopositive neurons may reflect their functional protective role.

4.4 Age-Related Changes in the Function of the Cochlear Nucleus

The age-related changes in the structure and neurochemistry of the CN (Sects. 4.2 and 4.3) are unsurprisingly accompanied by changes in the function of CN neurons. Willott et al. (1991) described age-related changes in the best frequencies and tuning properties of multiple and single units in the VCN and DCN, and in addition in the IC. In C57 mice, aging was accompanied by increased thresholds and deteriorated

frequency tuning, mostly in the VCN, whereas the DCN and IC units expressed smaller threshold increases and deterioration of frequency tuning. All of these age-related changes were observed only in C57 mice; in CBA mice little effects of age were found when comparing the response areas of neurons between young and old animals. The different influences of aging on neuronal thresholds and tuning in the VCN, DCN, and IC in C57 mice seem to be a unique observation that deserves to be verified in further experiments.

An important role in the function of the AVCN is played by glutamatergic transmission at the endbulb of the Held synapse between the auditory nerve fibers and bushy cells. A comprehensive study of synaptic transmission at the endbulb of Held was performed in DBA mice, a mice strain in which age-related changes already appear by the fourth week of age (Wang and Manis 2005). Synaptic transmission at the endbulb of Held in this strain was compared with synaptic transmission in CBA mice of the same age (i.e., between 17 and 65 days). Synaptic transmission in hearing-impaired high-frequency areas of the AVCN was altered in the older DBA mice. The frequency of spontaneous miniature excitatory postsynaptic currents (EPSCs) was substantially reduced, and miniature excitatory postsynaptic potentials were significantly slower and smaller in high-frequency regions of old (average age 45 days) DBA mice compared with tonotopically matched regions of young (average age 22 days) DBA mice. Young mice had a 30% higher synaptic release probability in high-frequency regions than the older ones.

More details are available about the influence of aging on synaptic transmission at the endbulb of Held in CBA mice, i.e., a model that corresponds more with human presbycusis. Synaptic transmission was assessed from bushy cells in mature (2–4 months) and aged (20–26 months) mice (Xie 2016; Xie and Manis 2017). The results showed that bushy neurons in old mice were more excitable and were able to fire spikes at a similar rate and timing to direct current injections as those in young mice. In response to synaptic inputs, however, bushy neurons from old mice fired spikes with a significantly decreased rate and reduced temporal precision to stimulus trains. Thus, it is believed that the transmission of auditory information at the endbulb of Held declines in both rate and timing during aging. Apparently the transmission of temporally precise information is degraded at the endbulb of Held during presbycusis.

Age-related changes in the inhibitory response properties of output neurons of the DCN have been described in rats (Caspary et al. 2005). Circuits within the DCN are supposed to encode temporally rich stimuli over a wide range of intensities, even when the signal is embedded in a background noise. Fusiform cells (DCN major output neurons) are under the control of a glycinergic inhibitory input from the vertical cells. Recording from units meeting fusiform cell criteria resulted in confirmation of the age-related decrease in the inhibition; in aged animals a significantly higher maximum discharge rate to tones at the unit characteristic frequency was found, along with significantly fewer nonmonotonic rate-level functions and an age-related change in temporal response properties, consistent with a decrease in glycinergic inhibition. In addition, single-unit recordings from aged inhibitory cartwheel cells in the DCN of rats (Caspary et al. 2006) revealed significantly higher thresholds,

increased spontaneous activity, and significantly altered rate-level functions characterized by hyperexcitability at higher intensities. Furthermore, aged cartwheel cells showed a significant reduction in offset suppression.

The age-related loss of inhibition compromises the ability of the DCN output neurons to encode sinusoidally amplitude-modulated (SAM) tones (Schatteman et al. 2008). This hypothesis was tested by recording from young and aged rat DCN putative fusiform cells, when stimulating with SAM tones at three modulation depths (100%, 50%, and 20%) at a 30-dB hearing level with the carrier frequency set to the unit's characteristic frequency. There were significant age-related changes present in the shape and peak vector strength of temporal modulation transfer functions (tMTFs), with no significant age-related changes in rate modulation transfer functions at the best modulation frequency. Putative fusiform neurons in young animals exhibited bandpass tMTFs for most SAM conditions, while the fusiform cells of aged animals exhibited significantly more low-pass or double-peaked tMTFs (Fig. 4.2). Age-related changes in SAM coding were similar to the changes observed with the receptor blockade of glycinergic inhibition onto fusiform cells and were consistent with the previously observed age-related loss of endogenous glycine levels and changes in normal adult glycine receptor function (see Sect. 4.3).

Age-related changes in the functional properties of CN neurons represent consequences of the structural and neurochemical changes. Loss of neurons, loss of synaptic connections, and decrease in the content of neurotransmitters and their receptors result in decreased firing rate of cochlear neurons and reduced temporal

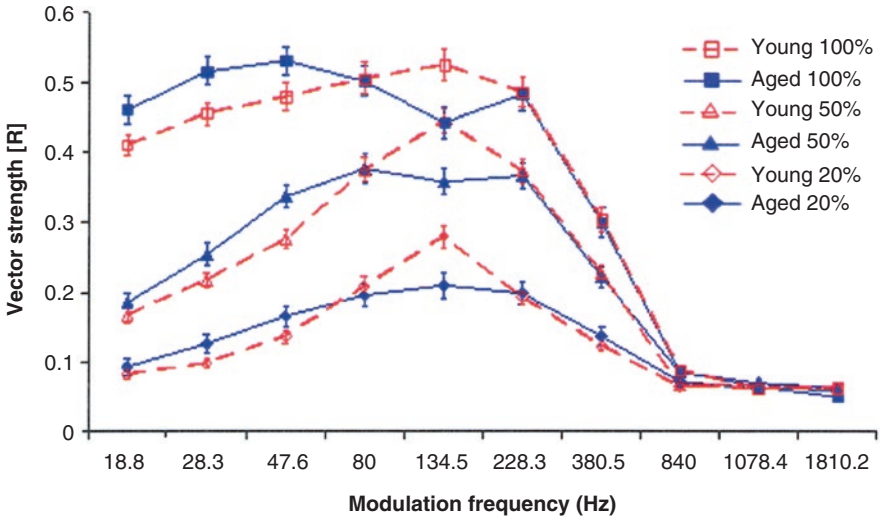

Fig. 4.2 Composite modulation transfer functions (vector strength) from young (93) and aged (88) fusiform cells at 100%, 50%, and 20% depth of modulation. Note the clear bandpass nature of the young temporal modulation transfer functions (tMTFs) at 50% and 20% modulation and the flatter and broader comparable tMTFs from aged fusiform cells. Error bars represent the SEM. (From Schatteman et al. 2008)

precision to stimulus trains, evident at the synapses between the incoming auditory nerve fibers and bushy cells in the AVCN. In addition, decreased glycinergic inhibition results in neurons of the DCN in higher maximum discharge rate to tones at the unit characteristic frequency, appearance of significantly fewer nonmonotonic rate-level functions, and an age-related change in the temporal response properties such as the ability of neurons to encode SAM tones.

4.5 Age-Related Changes in the Structure of the Superior Olivary Complex

The SOC consists of several nuclei—lateral superior olivary nucleus (LSO), medial superior olivary nucleus (MSO), medial nucleus of the trapezoid body (MNTB), ventral nucleus of the trapezoid body (VNTB), and superior paraolivary nucleus (SPO) (Schwartz 1992)—that play an important role, particularly in binaural hearing, thus delivering to the subject information about the acoustical space. Another important role of the SOC represents its feedback system of the olivocochlear bundle, which controls the function of both the IHCs and OHCs in the cochlea. It is well known that one of the sequelae of presbycusis is deterioration of spatial hearing. The questions remain as to what the changes occurring in the nuclei of the SOC during aging are contributing to age-related problems with spatial hearing, and whether or not aging significantly influences the function of the olivocochlear bundle.

No age-related changes were observed in the MSO and LSO, and in contrast to this, approximately 8% reduction with aging was found in the MNTB, when 3-month-old animals were compared with 24-month-old-Fischer 344 rats (Casey 1990). A similar age-related decline in the total number of neurons in the MNTB was found in C57 mice (O'Neill et al. 1997). The loss of neurons in the rat's MNTB appears to be strain specific, as in 24-month-old Sprague-Dawley rats, the loss was more pronounced (34%: Casey and Feldman 1982). In rats aged 24–33 months, there was also evidence of axonal and dendritic degeneration in the neuropil of MNTB (Casey and Feldman 1985). In young adult rats the mean percentage of the surface area of principal cells covered by synaptic terminals was 62%, while in aged animals it decreased to 44%. Only terminals derived from calyces of Held were lost in aged animals (Casey and Feldman 1988). Specific changes appear with aging in the MNTB of gerbils (Gleich and Strutz 2002). Specific spongiform lesions, similar to those observed in the VCN, are frequently found in the MNTB of gerbils older than 3 years. In addition to this, the mean MNTB neuronal soma size varies with age, decreasing from approximately 160 μm^2 in young adult animals to 130 μm^2 in old animals. In contrast to this, the age-related changes in the LSO were small, with the dimensions of the LSO and the number of glycine- and GABA-immunoreactive neurons not significantly different between young and old gerbils (Gleich et al. 2004). Only the size of glycine- and GABA-immunoreactive neurons was significantly reduced in the high-frequency part of the LSO.

Age-related decreases in the number of neurons are present in rats, mice, and gerbils mainly in the MNTB. They are combined with synaptic decreases and synaptic losses concerning the calyces of Held.

4.6 Age-Related Changes in the Neurochemistry of the Superior Olivary Complex

There is only limited information available on age-related neurochemical changes in the SOC. The changes in the number of calbindin D-28 k immunoreactive neurons in the MNTB occurring with aging were studied in CBA and C57 mice (O'Neill et al. 1997). Similarly, as in the CN, the total number of cells and the number of calbindin-immunopositive cells in the MNTB does not change with age in the CBA mice. In contrast to this, the total number of neurons in the MNTB of C57 mice decreases by 7% in old mice compared to young ones. The age-related decline is even more expressed in calbindin-immunopositive neurons. The mean number of calbindin-immunopositive neurons decreases by 11% in middle-aged, and by 15% in old C57 mice when compared with young controls. A similar situation as in calbindin immunoreactivity with respect to aging and mice strain was observed in the case of the potassium channel protein Kv3.1, which is expressed tonotopically in the rat MNTB (von Hehn et al. 2004). The tonotopic expression in the MNTB was present in both young and old CBA mice, whereas in the C57 it was evident only in 6-week-old mice, when hearing is normal. In contrast to this, at 8 months, when hearing is impaired in C57, the tonotopical gradient was abolished. A similar loss of tonotopic gradient with aging was observed in the expression of CREB, a cAMP response element-binding protein that regulates the transcription of Kv3.1. It is assumed, on the basis of this finding, that ongoing activity in the auditory brainstem neurons is necessary for the maintenance of Kv3.1 tonotopicity through the CREB pathway (von Hehn et al. 2004).

4.7 Age-Related Changes in the Function of the Superior Olivary Complex

Similar to the situation regarding neurochemistry, insufficient information is available about the influence of aging on the function of SOC neurons. For example, Finlayson and Caspary (1993) took recordings from LSO neurons in Fischer 344 rats and compared the reactions to sound in young and old animals. Most LSO principal cells exhibited ipsilateral excitation and contralateral inhibition of similar strength for similar stimuli, with no significant differences in many parameters of the neuronal activity between young and old animals. These parameters comprised rate-level functions generated by ipsilateral or contralateral stimuli, maximal

discharge rate conduction latencies, and measures of binaural function. Age-related differences were observed in the transmission synaptic properties at the C57 mouse calyx of Held, a large synapse on the principal cells of MNTB, when juvenile adults were compared with late middle-aged adults (Singh et al. 2018). The older animals exhibited a loss of temporal fidelity at the calyx synapse, which could result in binaural timing errors. In addition, short-term plasticity was also impaired, resulting in substantially decreased transmission and degraded circuit function. Interestingly, the synaptic transmission delays and defects in short-term plasticity were fully reversed in the older animals after application of acetyl-L-carnitine, an antiinflammatory agent that facilitates mitochondrial function.

4.8 Age-Related Changes in the Function of the Medial Olivocochlear Efferent System

The medial olivocochlear (MOC) efferent system, together with the lateral olivocochlear (LOC) efferent system, exerts important control over the function of the OHCs and IHCs. MOC efferents suppress the function of the OHCs in the ear contralateral to the SOC where their origin is located. It is possible to test the function of the MOC efferents by acoustical stimulation of the ear contralateral to the ear in which there are recorded otoacoustic emissions. The resulting reduction of the otoacoustic emissions is called contralateral suppression (CS). The neurons of the MOC efferents in rodents are located mainly in the VNTB, but also in other nuclei such as the dorsomedial preolivary nucleus, the medial nucleus of the trapezoid body, and the dorsal periolivary nucleus (Brown and Levine 2008). The olivocochlear bundle is supposed to play a role in reducing the masking effects of background noise, and therefore a hypothesis was formed that its deterioration might be a reason why elderly human listeners have problems with the processing of speech in background noise (Kim et al. 2002). A comparison of distortion product otoacoustic emissions (DPOAEs) in young adult, middle-aged, and older persons showed that DPOAE levels were lower in the older compared to the young group. However, CS already declined with age for the middle-aged group. In addition, CS in the 1- to 2-kHz range was greater than in the 4- to 6-kHz range for all ages, especially for the older group (Kim et al. 2002).

In CBA mice it was found that the DPOAEs decreased with age for mice in a way similar to that in humans, when correcting for the absolute difference in life spans (Jacobson et al. 2003). Similarly, the decline in CS already appears in the middle-aged animals and continues in old animals (Fig. 4.3). In C57BL/6 J mice, i.e., mice with accelerated aging of hearing, the deterioration of the MOC efferents function starts very early, already by 8 weeks of age (Zhu et al. 2007). The disappearance of CS is present particularly at middle (15–30 kHz) and high (30–45 kHz) frequencies. In addition, in the place of origin of the MOC bundle, in the ventral nucleus of the trapezoid body and in the dorsomedial periolivary nucleus, the neurons in the young

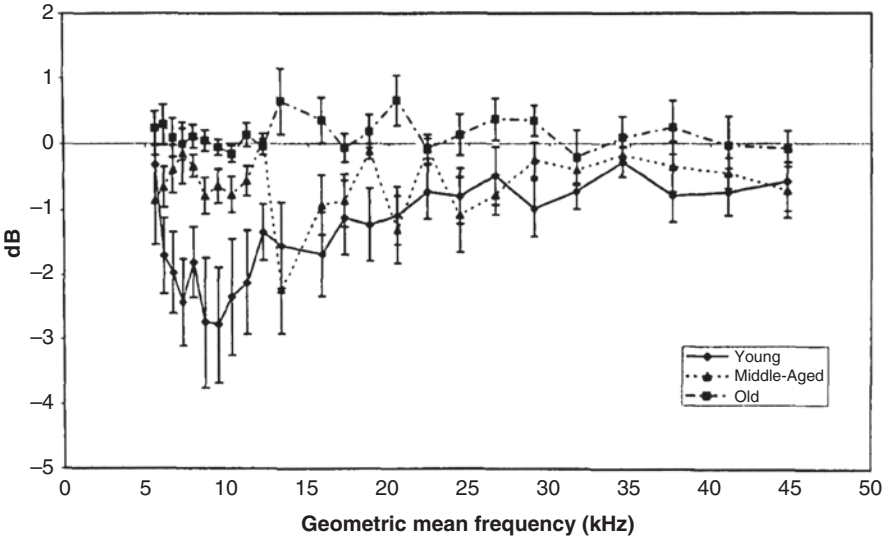

Fig. 4.3 Mean magnitude of contralateral suppression as a function of geometric mean frequency (kilohertz) in three groups of CBA mice. Contralateral suppression of distortion product otoacoustic emission (DPOAE) levels, mediated by the medial efferent olivocochlear system, declined with age. The most dramatic age-related decline occurred in middle age in the low frequencies, with further decline occurring in the aged group. Greater amounts of contralateral suppression are indicated by values that are more negative. The least suppression occurs in the high-frequency region, despite DPOAE amplitudes above 0 dB sound pressure level (SPL). Error bars represent SEM. (From Jacobson et al. 2003)

adult C57 mouse are smaller compared with the CBA mouse of the same age. Thus, in the C57 mouse, the MOC efferents function declines quickly, preceding the progression of peripheral age-related sensitivity deficits and hearing loss. Further proof for the early decline of the MOC efferents function was obtained when studying age-related changes in the Kv3.1b protein expression in the SOC of CBA mice (Zettel et al. 2007). Cellular optical density declines were found in the superior paraolivary nucleus, ventral nucleus of the trapezoid body, and lateral nucleus of the trapezoid body in middle-aged animals (15 months old). In addition, declines in the neuropil were observed with aging in the medial nucleus of the trapezoid body, in the lateral superior olive, and in the AVCN. The declines in Kv3.1b expression were correlated with declines in CS of DPOAE, which also declined by middle age. Kv3.1b knockout mice show poor MOC efferents function as compared to +/+ and +/− genotypes (Zettel et al. 2007).

Other evidence for the declining role of the MOC efferents in presbycusis was presented by Fu et al. (2010), who studied age-related synaptic loss of the MOC in the YFP-12 transgenic line, back-crossed to the C57BL/6 J genetic background. These mice have well-labeled synaptic terminals underneath both IHCs and OHCs. A dramatic synaptic loss between the MOC efferent fibers and OHCs was observed in older mice, which was independent of OHC status. Attention was also paid to

some details of the age-related changes of CS in humans, in a study by Konomi et al. (2014). In humans it was found that with aging, both the detectability and the degree of contralateral DPOAE suppression decrease and, in addition, the latency of the onset of DPOAE suppression increases.

Thus both in experimental animals and in humans, a significant deterioration of the function of the efferent olivocochlear bundle was demonstrated with aging. Further experiments will be necessary to prove or disprove the idea that this fact plays a major role in problems experienced with the processing of speech in background noise by older people with presbycusis.

4.9 Age-Related Changes in the Structure of the Inferior Colliculus

Information about the acoustical signal, after being processed in the CN, SOC, and the NLL (where almost nothing is known about age-related changes) reaches the major subcortical structure of the central auditory system: the IC. This part of the midbrain consists of three subdivisions: the central nucleus, the dorsal cortex and the external cortex (Morest and Oliver 1984). The lemniscal, tonotopic part of the IC is the central nucleus, where short-latency processing of the ascending information occurs, with the outputs being sent to the medial geniculate body. The dorsal and external cortices of the IC also project to the medial geniculate body, primarily to nontonotopic divisions. The IC cortices are major targets of the descending pathways from the auditory cortex (Druga and Syka 1984), and the external cortex in addition possesses strong connections with nonauditory structures such as the superior colliculus, substantia nigra, and somatosensory cortex (Syka and Radil-Weiss 1971; Aitkin et al. 1978).

In rodents, the IC represents a large structure, approximately 10 times larger in the number of neurons than the CN (Kulesza et al. 2002; Ouda et al. 2012b). With aging, the total number of neurons in the IC does not decline significantly; old adult rats of the Long–Evans strain showed only a 7% decline in the total number of IC neurons in comparison with young adults (Burianová et al. 2015). Similar differences were observed when the total number of neurons in young and old rats were compared in the medial geniculate body (−12%) and in the auditory cortex (−9%). Young and old Fischer 344 rats also do not show significant differences in the number of neurons in the central nucleus of the IC. However, a significant decline in the number of dendrites of both GABAergic and non-GABAergic neurons is present in the IC of old Fischer 344 rats. There are also reductions in the densities of GABA+ and GABA− synaptic terminals and synapses in 28-month-old rats relative to 3-month-olds. In GABA+ neurons, the distribution of synaptic terminals shifted with aging to dendrites of a larger caliber. Significant age-related changes were also not observed in the morphology of the IC in mice (Willott et al. 1994). Both in CBA/J mice and C57BL/6 J mice, age had no effect on the size of the IC, the size of

IC neurons, or the packing density of IC neurons and there was no evidence of a significant age-related neuronal loss. Thus, aging is not accompanied either in rats or mice by significant losses of IC neurons; however, the remaining neurons may have a smaller number of dendrites and synaptic terminals.

4.10 Age-Related Changes in the Neurochemistry of the Inferior Colliculus

In the first study addressing metabolism in the IC, 2-deoxy-D-glucose (2-DG) uptake in the IC of CBA and C57 mice was described (Willott et al. 1988c). It was found that there are no differences in 2-DG uptake between young and old mice of both species. However, the uptake was always larger than in the CN. Later, a seminal study showed that aging mostly influences metabolism of the major inhibitory neurotransmitter GABA in the IC (Caspary et al. 1990). It was demonstrated that in the central nucleus of the IC (CIC) in Fischer 344 rats, the number of GABA-immunoreactive neurons was reduced in old animals by 36% compared to their matched young adult controls. In addition, a significant age-related reduction in both basal and K^+-stimulated efflux of GABA from the CIC was found, whereas tissue content as well as the basal and evoked release of glutamate, aspartate, and [^{3}H]acetylcholine was similar between the two age groups. A similar reduction in the basal concentration of GABA in the CIC of rats with aging was observed by Banay-Schwartz et al. (1989). The idea of an age-related decline in GABA content in the IC was later supported by a series of further observations. The activity of the biosynthetic enzyme GAD was found to decline in the IC of old Fischer 344 rats by 31% when compared with young animals (Raza et al. 1994). Interestingly, the highest GAD activity was found in the CIC, intermediate in the NLL, and lowest in the CN. In agreement with the age-related decrease of GABA concentration and GAD activity, the $GABA_B$ receptor binding decreases in the IC of aged F344 rats (Milbrandt et al. 1994), whereas $GABA_A$ receptor binding does not change during the lifetime in the same structure (Milbrandt et al. 1996). The described age-related changes in the GABA neurotransmitter function in the IC of Fischer 344 rats were summarized by Caspary et al. (1995).

Age-related changes in GAD, the key enzyme for synthesis of GABA, in the IC were confirmed by Burianová et al. (2009), who measured these changes with several techniques, not only in the IC but also in the auditory and visual cortices. They used two strains of rats: Fischer 344 as a fast aging strain, and Long–Evans as a slowly aging strain, approaching the problem of aging in rats in a similar way to Willott and others, who used the C57 fast aging strain and CBA slowly aging strain of mice (for review of Fischer 344 rat and presbycusis see Syka 2010). While Long–Evans rats represent a strain with a relatively well preserved peripheral hearing function up to late senescence, a rapid and pronounced deterioration of hearing function with aging is found in Fisher 344 rats, resulting in larger hearing threshold

shifts, a decrease in the amplitude of click-evoked ABRs, a diminution of DPOAE, and a decrease in middle-ear compliance (Popelář et al. 2003, 2006). There are also differences in age-related changes between male and female Fischer 344 rats, with a deterioration of hearing function occurring more rapidly in males (Balogová et al. 2018). In spite of the expressed differences between Long–Evans and Fischer strains of rats, the age-related changes in the immunocytochemical markers in the IC were almost identical in both strains (Ouda and Syka 2012).

Results of quantitative immunocytochemical evaluation (Burianová et al. 2009) showed that the age-related decrease in the number of GAD-immunopositive neurons, although present in all analyzed structures, was significant in the Long–Evans strain for GAD65 only in the CIC, and for GAD67 in the AC. Decreases in the optical density of GAD-immunopositive neurons were expressed with aging, too. Protein analysis revealed a significant age-related decrease in the levels of GAD65 and GAD67 in Long–Evans rats (Fig. 4.4) in all three analyzed structures (IC, AC, visual cortex [VC]) with the most expressed decrease in the IC and AC. Different results from those shown in rats were observed in gerbils (Gleich et al. 2014). The number of GABAergic cells in the IC did not differ when young and old gerbils were compared, and as the IC was substantially shrunken due to aging, the density of GABAergic cells in old gerbils was found to be increased.

Age-related changes in glutamate, the main excitatory neurotransmitter in the auditory system, were rarely the subject of experimental studies. The gene expression of 68 glutamate-related genes was investigated by Tadros et al. (2007) in CBA mice. Two genes showed consistent differences: pyrroline-5-carboxylate synthetase enzyme (Pycs) displayed down-regulation with age, and a high-affinity glutamate transporter (Slc1a3) displayed up-regulation with age and hearing loss. The

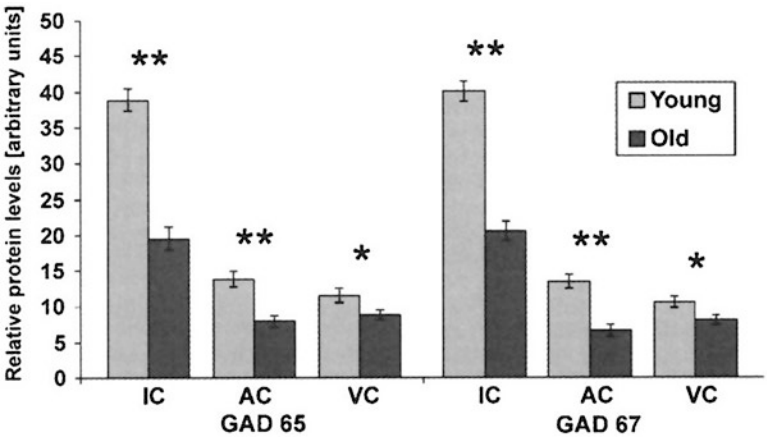

Fig. 4.4 Results of western blot GAD65 and GAD67 protein analysis in young and old Long–Evans rats. The error bar represents SEM. Arbitrary units were calculated as the ratio of the optical density of the examined protein and actin. AC, auditory cortex; GAD, glutamic acid decarboxylase; IC, inferior colliculus; VC, visual cortex (*$p < 0.05$, **$p < 0.01$). (From Burianová et al. 2009)

deficiency of Pycs in old age may result in glutamate increases, playing a role in the inducement of glutamate toxicity, whereas the up-regulation of Slc1a3 gene expression may reflect a cellular compensatory mechanism to protect against age-related glutamate and calcium excitotoxicity.

The calcium binding proteins parvalbumin (PV), calbindin (CB), and calretinin (CR) represent major fast calcium buffers in the central nervous system; they are supposed to protect neurons from insults that induce an elevation of intracellular Ca^{2+}. Their distribution seems to be complementary with the major occurrence of PV in the primary (tonotopic) and CB and CR in the nonprimary rat auditory regions. Specifically, in the rat IC, CB-immunoreactive (CB-ir) and CR-immunoreactive (CR-ir) neurons are abundant in the dorsal and external cortices and relatively rare in the CIC, while PV-immunoreactive (PV-ir) neurons are present in all three parts of the IC, with a predominant distribution in the CIC. The mutual colocalization of the PV, CB, and CR in one neuron is known to be relatively rare, as they mainly represent three distinct neuronal populations.

Age-related changes in PV, CB, and CR immunoreactivity were analyzed in the IC, medial geniculate body (MGB) and AC in both Long–Evans and Fischer 344 rats (Ouda et al. 2008, 2012a). In old Long–Evans rats (Fig. 4.5), the observed age-related changes in parvalbumin immunoreactivity were rather mild; the number of PV-ir neurons in the CIC was slightly increased, associated with an increase in optical density of PV-ir somas and a slight nonsignificant decrease in the mean neuronal volumes. In Fischer 344 rats a significant decrease in the mean PV-neuronal volume in the CIC and a decrease in the number of PV-ir neurons in the AC was observed

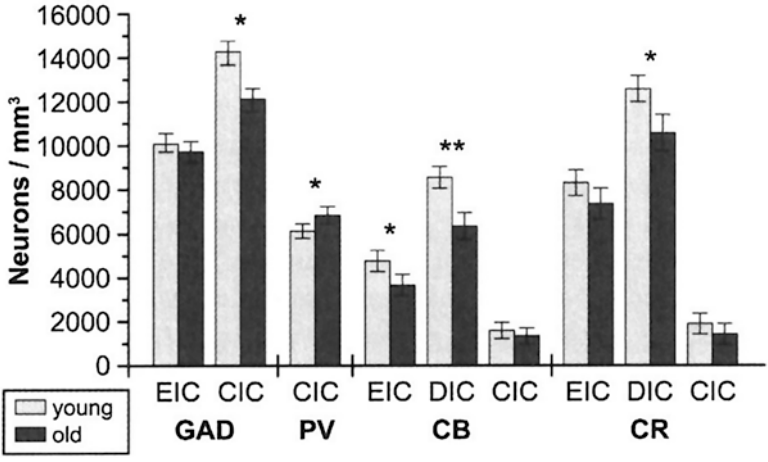

Fig. 4.5 The numerical density of GAD-ir, PV-ir, CB-ir, and CR-ir neurons in the external and dorsal cortices and in the central nucleus of the inferior colliculus (IC) in young and old Long–Evans rats. CB, calbindin; CIC, central nucleus of the inferior colliculus; CR, calretinin; DIC, dorsal cortex of the inferior colliculus; EIC, external cortex of the inferior colliculus; GAD glutamic acid decarboxylase, isoform 67; PV, parvalbumin. The error bars represent SEM. ($^{*}p < 0.05$, $^{**}p < 0.01$). (From Ouda and Syka 2012)

(Ouda et al. 2008). The age-related changes in calbindin and calretinin immunoreactivity had a fairly similar pattern and were relatively uniform, regardless of the examined rat strain (Ouda et al. 2012a). Significant changes comprised a decrease in the number of CB-ir neurons in the dorsal and external cortices of the IC in both Long–Evans (Fig. 4.5) and Fischer 344 rats, accompanied by significant decreases of CB-ir neurons in the MGB. In most of these structures, a significant decline in the average volume of CB-ir neuronal somas was also present. Age-related changes in CR-immunoreactivity were less expressed, with a declining number of CR-ir neurons in the dorsal cortex of the inferior colliculus (DIC) in both rat strains and a significant decrease in the average volume of CR-ir neuronal somas in the external cortex of the inferior colliculus (EIC) and DIC, also in both rat strains. Age-related changes in immunoreactivity were confirmed when CB and CR proteins were analyzed with the western blot technique, in young and old rats. Almost 50% decreases in CB proteins were observed in aged rats in both the IC and AC, whereas CR protein decreases were found to be significant only in the IC (Ouda et al. 2012a).

A similar analysis of age-related changes in the number and content of calbindin- and calretinin-immunoreactive neurons in the IC was performed in C57Bl/6 and CBA/CaJ strains of mice (Zettel et al. 1997). In the case of calbindin, the results were similar to those in the rat's IC, where aging resulted in a decrease in the number of calbindin-ir neurons both in CBA and C57 mice. The results in the case of calretinin-ir neurons were different; the IC dorsal cortex, lateral nucleus, and the nucleus of the lateral commissure showed an age-related increase in the number of calretinin-ir neurons in CBA mice, whereas the numbers of calretinin-ir neurons in the IC of old C57 mice were not different from those in the young animals. However, early bilateral deafening was able to prevent the calretinin up-regulation in the dorsal cortex of the IC in aged CBA mice (Zettel et al. 2001), thus supporting the hypothesis that calretinin up-regulation depends on sound-evoked activity. The calcium binding proteins represent major fast cytoplasmic calcium buffers in the central nervous system, and thus protect neurons from insults that induce an elevation of intracellular Ca^{2+}. The disruption of calcium homeostasis in neurons may be involved in both the impairments that accompany normal aging and also in different pathologies associated with age-related disorders. It is interesting therefore that calcium-binding mutant mice are not only able to survive, but also do not display significant changes in phenotype, either in the general morphology of the nervous system or their behavior under normal housing conditions (Schwaller et al. 1999). For example, parvalbumin deficient (PV−/−) mice have normal hearing thresholds, with detectable differences in acoustic startle reaction and prepulse inhibition in comparison with control mice (Popelář et al. 2013). These differences are apparently produced by specific changes in neuronal circuits, mainly inhibitory, in the auditory centers of the parvalbumin-deficient mouse. For more details about age-related changes in the neurochemistry of the IC see Ouda and Syka (2012).

In addition to the age-related changes of GAD and calcium–binding proteins, there are also age-related changes in the number of SMI-32-immunoreactive neurons and levels of nonphosphorylated neurofilament proteins in the IC, MGB, and AC of Long–Evans and Fischer 344 rats (Burianová et al. 2015). In all mentioned

structures, the number of SMI-32-immunoreactive neurons as well as the protein levels decreased significantly with aging. Although SMI-32-ir neurons usually constitute a minority of the neuronal population in a particular central auditory structure (Ouda et al. 2012b), their vulnerability with aging (Veeranna et al. 2011) may play an important role in carrying and processing fast auditory signals. For example, a reduction in the speed of speech processing is one of the important signs of presbycusis (Wingfield et al. 1985).

The results of neurochemical analysis show that dominant age-related changes in the IC of mice and rats mainly involve the inhibitory transmitter GABA that declines with aging in individual subnuclei of the IC to different extents. The decreases are present not only in the GAD activity and in levels of GAD proteins but also for GABA receptors, particularly the $GABA_B$ receptor. Similarly, although less uniform, there are age-related changes in the activity of calcium-binding proteins, with a majority of these changes representing decreases, whereas in some cases CBP activity and level may increase. The decreases with aging also involve neurons expressing nonphosphorylated neurofilament proteins: SMI-32 neurons.

4.11 Age-Related Changes in the Function of the Inferior Colliculus

The IC represents an important integrative nucleus of the central auditory system with multiple ascending as well as descending inputs. The first attempts to understand the effects of aging on the function of the IC originated relatively early, with recording of single unit activity in young and old CBA/J mice (Willott et al. 1988a) and C57BL/6 J mice (Willott et al. 1988b). The differences in response properties to sound stimuli, which were found both with respect to age and strain, were relatively small. The spontaneous activity in the IC in both strains increased with age; in CBA mice this was mostly in the ventral high-frequency part, and in C57, predominantly in the central IC nucleus. However, major response characteristics, such as types of poststimulus-time histogram or typical parameters of the response areas (range, upper frequency range, best frequency, and rate-best frequency) did not essentially change with age in either strain. In the fast aging C57 mice, a decrease in the percentage of neurons with nonmonotonic rate–level function was observed, suggesting that a decrease in inhibition may occur with aging in this strain.

When comparing ABRs in young and old Fischer 344 rats (Backoff and Caspary 1994) there were elevated ABR click thresholds in old animals, reflected by shifts in the latency-intensity curves. With increased stimulation rates, aged rats exhibited prolonged wave 4 and 5 latencies, i.e., latencies of waves originating in or around the IC. In addition, the morphology of waves was degraded and peak amplitudes were generally reduced in old rats. Single-unit recording of frequency response areas in the IC of Fischer 344 rats (Palombi and Caspary 1996a) mostly confirmed the changes observed in the IC of aged mice (Willott et al. 1988a, b); no differences

in comparison with young animals were found in spontaneous activity, first spike latency, dynamic range, percentage of units with nonmonotonic contralateral CF tone rate/intensity functions, or percentage of units sensitive to change in CF tone presentation rate. Differences were observed between age-related changes in the units of CIC and the external cortex of the IC (EIC), for example the percentage of units classified as having nonmonotonic rate/intensity functions decreased with age in the CIC but increased in the EIC. As Palombi and Caspary (1996a, p. 3114) suggested, "the compensatory mechanisms are highly active in sensory systems as animals age. Despite deficits that lead to reduced input to the IC and neurochemical changes affecting neurotransmitter levels, IC neurons in aged rats are able to respond to most simple auditory stimuli in a fashion quite similar to that observed in young rats."

As it is known that one of the typical signs of presbycusis is deteriorated spatial hearing, a question naturally arose as to whether any differences exist between young and old animals in the responsiveness of IC neurons to binaural stimuli. Surprisingly, Palombi and Caspary (1996b) did not find statistically supported differences when they compared the responses of young and old Fisher 344 rat IC neurons to binaural tonal stimuli. They noticed only a shift in the distribution of binaural rate/intensity functions with age, which included a reduction in the percentage of units classified as E/I (excited by contralateral stimulation/ipsilaterally inhibited during binaural stimulation) and an increase with age in the percentage of units classified as E/f (excited by contralateral stimulation/further facilitated by the addition of low-intensity ipsilateral stimulation, but inhibited by higher intensity ipsilateral stimulation). The differences were present only in the CIC, not in the EIC.

Deteriorated perception of complex sound stimuli, such as speech, accompanies aging in humans and may be connected with problems occurring in the perception of temporal properties of sound stimuli such as the perception of minimal gaps in noise. The detection of brief silent intervals in an ongoing sound is a simple but efficient method for the assessment of auditory temporal resolution. Age-related alterations in the processing of temporal sound features were studied in the IC of young and old CBA mice by recording the responses of IC neurons to silent gaps cmbedded in noise (Walton et al. 1998). The shortest minimal gap thresholds (MGTs) were found, regardless of age, in phasic units, which react with a brief onset reaction. They were found both in young and old animals, and the proportion of neurons exhibiting the shortest MGTs was much lower in old mice, regardless of the presentation level. In addition, in the majority of phasic units, the recovery of response to the stimulus after the silent gap was of a lower magnitude and much slower in the units from old mice. Overall, these results suggested that at the level of single units in the auditory midbrain, signs of deteriorated processing of temporal sound features in old CBA mice can be found. The deterioration in the processing of temporal sound features starts in CBA mice relatively early (Williamson et al. 2016). Middle aged (15–18 months old) mice already exhibit minor changes in ABR peak latency and decreased peak amplitude in response to temporal gaps, in comparison with the young adult group (age 3–4 months).

The age-related deterioration in the processing of minimal gaps is possible to study not only with electrophysiological methods, but also behaviorally. Šuta et al. (2011) used the conditional avoidance procedure to assess the effects of aging on gap detection thresholds in Long–Evans rats. The values of the gap detection threshold (GDT) and gap duration difference limen in old rats were found to be about two times larger in comparison with young adult rats. The authors also recorded, in the same group of animals, middle latency responses (MLRs) that are supposed to be generated by the activity of higher parts of the auditory pathway (Barth and Di 1990). The MLR to a click train in old rats exhibited a significantly faster reduction in amplitude with increasing stimulation rate, in comparison to young adult rats. None of the age-related changes in these parameters, characterizing auditory temporal resolution, correlated with the degree of age-related hearing loss, thus supporting the relative independency of age-related processes occurring in the peripheral and central parts of the auditory system. The age-related deterioration in the processing of acoustical stimuli is also possible to demonstrate with the recording of acoustic startle reflex (ASR) and prepulse inhibition of the startle reflex (Rybalko et al. 2012). Both the amplitude of startle reflex and the efficiency of the prepulse inhibition decreases with aging, both in Long–Evans and Fischer 344 rats, and the decrease is faster in the Fischer 344 rat strain. Similarly, as in the case of GDT and MLR, no significant relationship between hearing thresholds and the ASR amplitudes was found within any age group.

Another approach for assessing age-related changes in the processing of temporal parameters of sound in the auditory system represents a study of differences in the neural coding of envelope periodicities. Significant differences were found between the responses of single units in the IC of young and old CBA mice when stimulated by SAM noise carriers (Walton et al. 2002). The main finding showed an overall increase in the response rate to SAM noise carriers and a decrease in the median upper cutoff in units from old mice. The differences were found both at best modulation frequency for rate (rBMF) when the median spike counts for units in old animals was 1.63 times greater, and at best modulation frequency for synchronization (sBMF) when the medial spike count was 2.29 times greater than in old animals. The young adult distribution of rBMF was found to extend to higher modulation frequencies than the old, with 36% of units having rBMF higher than 100 Hz, compared with only 12.5% units of the old animals.

Local field potentials (LFPs) and spikes in the IC of young and old Fischer 344 rats were recorded with the aim to investigate how aging affects the neural representations of white noise carriers that were amplitude modulated at three different modulation rates (45 Hz, 128 Hz, and 256 Hz) using five different envelope shapes (Herrmann et al. 2017). The results show that envelope shapes up to 256-Hz modulation rates are represented in the neural synchronization phase lags in younger and older animals. For the local field potentials, responses were significantly larger for younger compared to older rats for all three modulation rates, and, in contrast, firing rates were not different between age groups. These experiments were preceded in the same group by the building of a computational model of inferior colliculus responses to amplitude-modulated sounds in young and aged rats

(Rabang et al. 2012). The model was used to make predictions about the consequences of reduction in inhibition for age-related loss of temporal processing due to a reduction in inhibitory neurotransmitters with age.

In addition to the ABR responses already discussed for brief stimuli, population brainstem and midbrain responses elicited by longer periodic acoustical stimuli lasting for tens to hundreds of milliseconds are either frequency following responses (FFRs), tracking low carrier frequencies, or the amplitude modulation following responses (AMFRs), tracking changes in the modulation envelope. The FFRs and AMFRs represent the summed synchronized population responses of spiking activity and the synaptic potentials of neurons in the brainstem and midbrain. The assessment of AMFRs with SAM tones in Fischer 344 rats showed that the overall shapes and cutoff frequencies of the AMFR tMTFs were similar between young and aged rats (Parthasarathy et al. 2010). However, the AMFR amplitudes varied significantly between young and aged animals for SAM stimuli in the presence of background noise, depending on the modulation frequency used and the signal to noise ratio (Fig. 4.6). The results of the experiments help to explain problems in human listeners when recognizing speech superimposed upon a background of other speakers or background noise, in contrast to a situation when recognizing isolated speech sounds.

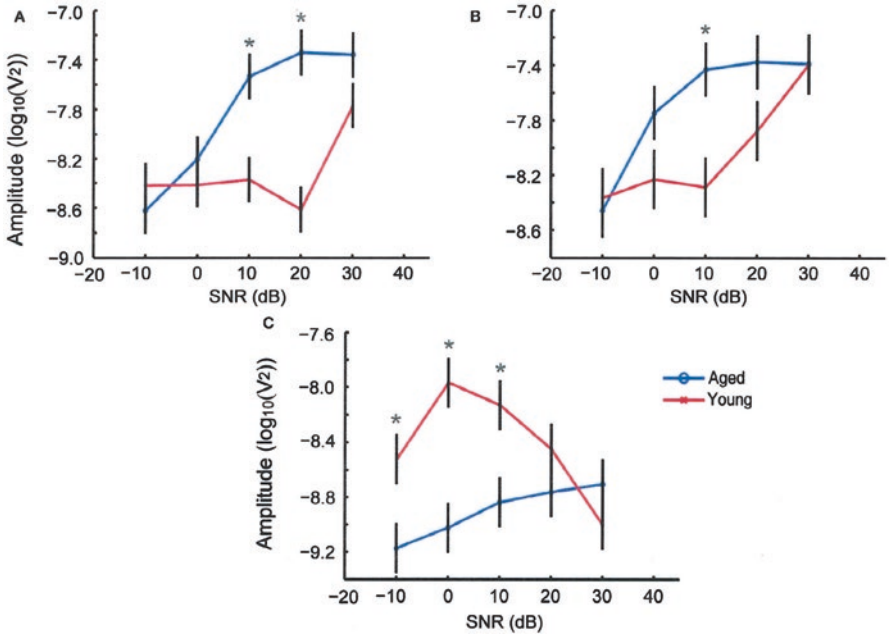

Fig. 4.6 Changes in amplitude modulation following response (AMFR) amplitudes for sinusoidally amplitude-modulated (SAM) stimuli presented with simultaneous background noise are dependent on age, modulation frequency, and signal-to-noise ratio (SNR). (**A–C**) Modulation frequencies 256, 512, and 1024 Hz respectively. The *x*-axis indicates SNR, and the *y*-axis indicates the least square mean ± SE of the fast Fourier transform (FFT) amplitudes. Asterisks indicate statistically significant difference in least square means ($P < 0.05$, MANOVA). (From Parthasarathy et al. 2010)

Further experiments by Parthasarathy and Bartlett (2011) in Fischer 344 rats showed that the amplitudes of AMFRs depend on the modulation depth. They found a monotonic decrease in AMFR amplitudes with decreases in modulation depths across age for SAM stimuli, similar to findings in human subjects (He et al. 2008). Consistent with IC LFPs, AMFRs were smaller for more rapid AM frequencies (>100 Hz) in older animals. Similar results were obtained when instead of SAM stimuli, sinusoidally frequency-modulated tones were used. However, when they recorded responses to ramped or damped amplitude modulation stimuli, the results were different for young and old rats; the aged animals showed significantly lower response amplitudes for ramped stimuli but not for damped stimuli. In addition, cross correlating the responses with the ramped, symmetrical, or damped stimulus envelopes revealed a decreased fidelity in encoding envelope shapes with age. These results suggested that age-related temporal processing deficits are possible to detect when using stimuli with reduced modulation depths or when discriminating different envelope shapes, but not for slower, salient stimuli.

The contribution of dysfunction of the peripheral and central parts of the auditory system to age-related changes in auditory temporal processing remains one of the cardinal questions that need to be answered by contemporary research. Lai et al. (2017) tried to contribute to the solution of this problem by testing different ways of manipulating stimulus intensities to attain comparable peripheral or central neural activation for auditory evoked potential recordings. They compared envelope-following responses (EFRs) of young and aged Fischer 344 rats when sound levels were matched either according to wave 1 amplitudes of ABRs elicited by 8-kHz tones or EFRs amplitudes evoked by SAM tones at 100% depth. The first method was used as an indicator of peripheral matching, while the second method was used for central matching. For matched wave 1, no age-related differences were observed in wave 5 amplitudes. Negligible differences in EFRs were observed between young and aged animals at both equivalent peripheral and central activations for SAM depth processing at the modulation frequencies tested. However, EFRs recorded in silence were enhanced with aging at 100% but not at the 25% depth that is consistent with enhanced central gain in aging and consistent with the reduced GABAergic inhibition discussed in Sect. 4.9.

The central auditory system can modify the strength of the sound-evoked neural response, a phenomenon referred to as central gain. Gain changes are well documented after traumatic noise exposure (Syka et al. 1994; Salvi et al. 2000), after prolonged low-level noise exposure (Sheppard et al. 2017) and even after near-complete cochlear denervation (Chambers et al. 2016). Increased gain of neural network activity in the IC was recently demonstrated also in association with aging (Parthasarathy et al. 2019). The authors observed an age-related increase in sensitivity to the sound's onset and temporal regularity in the spiking output of IC neurons, relative to their synaptic input, represented by local field potentials. Specifically, synchronization to the periodicity envelope of speech was enhanced for spiking activity of populations of IC neurons in aged rats in comparison with controls.

In summary, aging does not fundamentally change the responsiveness of IC neurons to simple acoustical stimuli; however, some differences between old and young

animals are noticeable. Spontaneous activity may increase with aging and, in agreement with decreased inhibition, the presence of nonmonotonic rate-level functions may also decrease. In addition, slight differences in the responsiveness to binaural stimuli may occur. However, significant differences are present in the processing of temporal parameters of acoustical signals; for example, deterioration is present in the processing of minimal gaps, expressed as an increase in the gap detection threshold and gap duration differences limens. Single units from old mice respond with an increased response rate to SAM noise carriers and have a decreased median upper cutoff in comparison with the units from young mice. Similarly, amplitudes of amplitude modulation following responses vary significantly between young and aged rats for SAM stimuli in the presence of background noise, depending on the modulation frequency used and the signal-to-noise ratio. Aged rats also show significantly lower response amplitudes for ramped amplitude-modulated stimuli but not for damped stimuli. Local field potentials to amplitude-modulated noise carriers are significantly larger for younger compared to older rats and in contrast, firing rates of IC neurons are not different between age groups.

4.12 Chapter Summary

Aging is in principle accompanied by brain atrophy. However, this atrophy may be expressed differently in individual parts of the brain of experimental animals. In the CN of mice and rats, the overall number of neurons decreases. Another major effect in CN is decreasing glycinergic inhibition, which may negatively influence temporal processing of acoustical information in the cochlear nuclei. Besides age-related decrease in the glycinergic inhibition the cochlear nuclei exhibit an increase in the number of neurons containing calcium-binding proteins, particularly parvalbumin and calbindin. This increase appears to be compensatory, to counterbalance the loss in the number and function of incoming auditory nerve fibers. The deterioration of temporal processing of acoustical signals is evident from the age-related change of bandpass to lowpass temporal modulation transfer function in neurons of the cochlear nuclei when recording responses to amplitude-modulated tones.

Relatively limited information exists about age-related changes in the SOC. Loss of transmission fidelity on large MNTB synapses, found in old animals, may contribute to the problems with binaural hearing observed with aging, but more data in this direction are necessary. More information is available about age-related changes in the function of the MOC efferent system. The decline in the function of the MOC bundle, that is possible to demonstrate by contralateral suppression of DPOAEs, appears relatively early, thus preceding changes in auditory sensitivity. It is possible that this early decline in function represents the basis of age-related problems with hearing of acoustical signals, like speech, in a noisy environment.

The loss of neurons in the IC with aging in both mice and rats is relatively small; major loss concerns inhibitory GABAergic neurons, with their dendrites and their receptors. Aging influences the number of calcium-binding neurons differently in

the IC in comparison with the CN. The numbers of parvalbumin-positive neurons slightly increase, whereas the occurrence of calbindin- and calretinin-positive neurons decreases with age. The comparison of responses of IC neurons to traditional stimuli such as pure tones or noise did not show expressed differences between young and old animals; however, responses to acoustical stimuli with a complex temporal structure such as silent gaps in noise, or SAM sounds, are significantly influenced by aging in old mice or rats, showing a deterioration of responsiveness to such stimuli, with a shift of responsiveness to less frequent, less synchronized, and longer stimuli. Central auditory nuclei, such as IC, respond to age-related deafferentation with a compensatory plasticity, in the form of altered gain.

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Compliance with Ethics Requirements Josef Syka declares that he has no conflict of interest.

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Chapter 5
Age-Related Changes in the Primate Auditory Cortex

Gregg Recanzone

Abstract Age-related hearing deficits are a serious health concern, afflicting approximately half of the geriatric population. Previous anatomical and physiological studies in rodent models have suggested that aging causes a decreased afferent drive from the cochlea, which is then compensated for by changing the balance of excitation and inhibition throughout the subcortical auditory axis. Few studies have investigated this in the nonhuman primate, and even fewer studies have examined changes at the cortical level in nonrodent species. This chapter reviews evidence from the macaque monkey at the subcortical level examining the distribution of calcium-binding and calcium-associated proteins. It then reviews electrophysiological studies on how the young and old cortical neurons process spatial and temporal information from both core and belt areas of auditory cortex. The findings show that a similar age-related change in calcium-binding protein expression occurs in the macaque as seen in the rodent. In addition, a change in the excitatory and inhibitory balance could account for higher spontaneous and driven responses, broadening of spatial tuning, and decreased temporal fidelity in both core and belt auditory cortical neurons in aged animals. These results are consistent with the spatial and temporal processing deficits seen in age-related hearing loss.

Keywords A1 · Caudolateral field · Cochlear nucleus · Inferior colliculus · Macaque · Medial geniculate nucleus · NADPHd · Parvalbumin · Spatial tuning · Superior olivary complex · Temporal tuning

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5.1 Introduction

Age-related hearing loss is a prominent malady of the geriatric population, afflicting more than 50% of the geriatric population older than 75 years of age (Humes et al. 2009, 2012; see Helfer and Bartlett, Chap. 1; Deal, Reed, and Lin, Chap. 8; Humes, Pichora-Fuller, and Hickson, Chap. 11). In spite of this prevalence, very little is currently understood about the consequences of these deficits on the central nervous system, particularly in the cerebral cortex. This is somewhat surprising, given that the cerebral cortex is critical for normal auditory perception. Studies in nonhuman primates have shown that there are numerous parallels with human perceptual deficits, and most experiments show results consistent with those from rodent animal models. What remains unclear, unfortunately, is how much of the perceptual deficits are the result of deficits manifest at the periphery, brainstem, midbrain, and thalamus, which are then inherited by the cerebral cortex. Further, how cortical responses are altered that give rise to both normal perception and then altered perceptions with natural aging is not entirely clear. This chapter briefly reviews the subcortical changes recently described in nonhuman primates, as well as several studies of age-related affects in auditory cortical function, and how these results fit into the larger body of rodent literature.

5.1.1 Psychophysically Measured Age-Related Hearing Deficits

While hearing loss is well documented to occur in increasing numbers as individuals age, many individuals retain relatively normal hearing throughout life. Nonetheless, many of these individuals, with "normal" audiograms, defined by being within 20 dB of thresholds in young individuals, still suffer hearing deficits. This manifestation of "hidden hearing loss" has several potential causes, both peripheral and central, which are explored throughout this chapter as well as others in this volume (Gordon-Salant and Wingfield, Chap. 9; Kuchinsky and Vaden, Chap. 10; Humes, Chap. 11).

Regardless of peripheral hearing status, it is also well documented that aged individuals have more difficulty in understanding what they do hear, especially in a noisy environment (Frisina and Frisina 1997; Füllgrabe et al. 2015; see Gordon-Salant and Wingfield, Chap. 9). The most common complaint is that they have difficulty processing speech stimuli in noisy environments, giving rise to the complaint "I can hear you, but I can't understand what you are saying" (see also Kuchinsky and Vaden, Chap. 10; Humes, Chap. 11). In the laboratory, it has been revealed that aged individuals have deficits in localizing sounds in space (Dobreva et al. 2011; Freigang et al. 2015) and processing temporal information, such as gaps in noise (Allen et al. 2003; Palmer and Musiek 2014), and other temporally based tasks (e.g., Ozmeral et al. 2016; see Walton 2010). Thus, both spatial and temporal processing deficits can occur, and these are at least in large part centrally mediated, as they

occur in individuals with normal hearing, or using stimuli that are matched in sensation level between the young and aged participants.

A major question in hearing and aging, then, is how to assign different deficits, or types of deficits, to changes in different structures. The simplest remedy would be to amplify the signal from the periphery such that the central nervous system gets the same signal as when the individual was younger (see Humes et al., Chap. 11). However, there are also clear changes in the auditory brainstem, midbrain, and thalamus (see Ouda et al. 2015; Gray and Recanzone 2017) that undoubtedly contribute to processing deficits as well. Finally, all of these changes are necessarily inherited by the cerebral cortex, where the site of auditory perception occurs, and therefore are of critical importance in understanding age-related hearing deficits. Unfortunately, we know very little about the age-related effects on auditory cortical function, and what consequences the different peripheral and subcortical changes have on auditory cortical processing. This is due, at least in part, on the limited number of animal models, which have primarily been restricted to rodents.

5.1.2 The Macaque Monkey as an Animal Model of Age-Related Hearing Loss

A hallmark animal model for understanding the cerebral cortical contributions to perception is the macaque monkey (Spillmann 2009; Pei and Bensmaia 2014). The macaque monkey ages at approximately three times that of the human, so a 22-year-old monkey is roughly equivalent to a 66-year-old human and would be considered geriatric (see Davis and Leathers 1985). There is good evidence that the aging monkey shows cochlear deficits similar to those of the human (Engle et al. 2013; Valero et al. 2017) and suffers from similar age-related audiometric hearing deficits (Ng et al. 2015). This animal model has been effective in extending our understanding of auditory cortical processing (i.e., Recanzone and Sutter 2008; Recanzone and Cohen 2010), yet little has been done to better understand the effects of aging on these processes, until fairly recently.

5.2 Effects on Subcortical Structures

A multitude of studies have provided evidence, primarily in rodents but increasingly in nonhuman primates, that natural aging results in a myriad of changes throughout the ascending auditory pathway (i.e., see Ouda et al. 2015; Gray and Recanzone 2017). These changes, initiated in the cochlea, will undoubtedly be inherited by cortical neurons. While different aspects of acoustic signals can be extracted from the peripheral signal, information cannot be added. Therefore, it is necessary that the fidelity of the incoming signal remain as precise as possible at each stage of acoustic processing.

5.2.1 Peripheral Effects

Historically, age-related hearing loss, or presbycusis, was believed to be the result of histopathological changes in the cochlea (Ramadan and Schuknecht 1989; Schuknecht and Gacek 1993). These were manifest as loss of the inner hair cells (IHCs; a full list of abbreviations used in this chapter is provided in Table 5.1), outer hair cells (OHCs), or spiral ganglion cells, or as a reduction in the stria vascularis (see Ohlemiller, Chap. 3). It was believed that these different histopathologies corresponded to different changes in the audiogram. Animal studies have indicated that this is not as straightforward as previously believed. Figure 5.1 shows the results from one histological study in macaque monkeys (Engle et al. 2013; Ng et al. 2015). Eight different monkeys of varying ages had their hearing thresholds measured using the auditory brainstem response (ABR), an electrophysiological measure of early auditory neural function. Multiple animals were tested, and while there was considerable variability between individuals (Ng et al. 2015), eight animals were selected that showed a progressive increase in hearing thresholds with age (Engle

Table 5.1 Abbreviations used in this chapter

A1	primary auditory cortex
ABR	auditory brainstem response
AL	anterior lateral area
AM	amplitude-modulated
AVCN	anterior ventral division
CB	calbindin
CL	caudolateral area
CR	calretinin
DCN	dorsal cochclear nucleus
GABA	γ-aminobutyric acid
IC	inferior colliculus
IHC	inner hair cell
ML	medial lateral area
MSO	medial superior olivary
NADPHd	nicotinamide adenine dinucleotide phosphate diaphorase
NO	nitric oxide
OHC	outer hair cell
PTA	pure-tone average
PV	parvalbumin
PVCN	posterior ventral cochlear nucleus
R	rostral area
RT	rostrotemporal area
VS	vector strength
VSpp	phase-projected vector strength

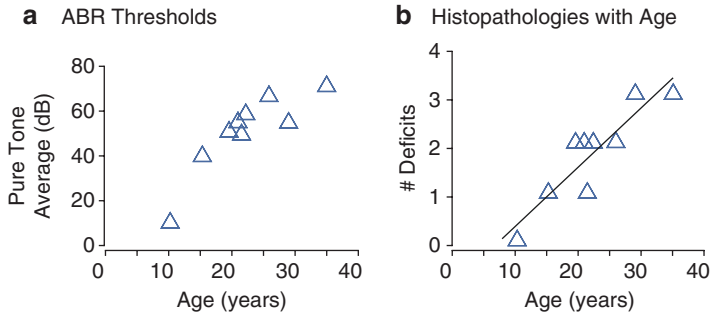

Fig. 5.1 Correlation between age, hearing loss, and cochlear pathologies. (**a**) Pure-tone averages taken from thresholds measured using the auditory brainstem response (ABR) normalized to the lowest thresholds measured from young monkeys (Ng et al. 2015). Selected monkeys had progressively greater thresholds (poorer hearing) as a function of age. (**b**) Number of histopathologies measured in the same monkeys as a function of age. Histopathologies included inner hair cell loss, outer hair cell loss, decreased spiral ganglion cells, and stria vascularis thickness. It was the number, not the type, of histopathologies that increase with age and hearing loss. (Data adapted from Engle et al. 2013)

et al. 2013). The pure-tone average (PTA) was taken as the average ABR threshold to seven tones ranging from 0.5 kHz to 16 kHz in one-octave steps (Fig. 5.1a). The cochlea from these same animals then underwent histological processing at both the light and electron microscopic levels to investigate the presence of four different cochlear histopathologies. The first was the loss of IHCs, which was simply counted as the presence or absence of the cells within different turns of the cochlea. The second was the presence of OHCs, measured in the same way. The third was the extent of spiral ganglion cell loss, and, finally, the thickness of the stria vascularis was also measured. When the progression of any one deficit was measured as a function of age, there were only weak correlations for most metrics, and they were not always necessarily consistent across the linear extent of the cochlea. One exception was with the loss of spiral ganglion cells, which was consistent across the cochlea. However, the strongest correlation of cochlear deficits with age was not with any single parameter, but rather with the number of different deficits occurring in different individuals (Fig. 5.1b). This indicates that there is not necessarily a steady progression of cochlear deficits that can result in increased hearing thresholds. Rather, different deficits that could arise from very different mechanisms can all additively decrease hearing function.

It has also been revealed that morphological changes occur that can be much more subtle, wherein the hair cells and spiral ganglion cells are intact, yet the ribbon synapses between the hair cells and spiral ganglion cells are missing (see Kujawa and Liberman 2015). This was initially observed in mice and hamsters, but has subsequently been observed in both macaque monkeys (Valero et al. 2017) and humans (Viana et al. 2015). While it is unfortunate that the Engle et al. (2013) study did not include investigation of ribbon synapses, presumably they did show a similar reduction as a function of age. These findings indicate that there is a decreased afferent

drive from the cochlea as a natural consequence of aging, and therefore even those individuals with audiograms considered within the "normal" limits are still effectively reducing the input to the central auditory system. This has important consequences for two reasons. First, it suggests that this decreased afferent drive will initiate a variety of neurochemical changes throughout the ascending auditory system (reviewed in Sect. 5.2.2). Second, this reduced drive potentially can directly influence both spatial and temporal processing, hallmark deficits in age-related hearing loss.

5.2.2 Anatomical Studies of Subcortical Areas

Previous studies in rodent models have indicated that there are dramatic changes in the expression of different calcium-binding proteins throughout the ascending auditory system as a function of age (Ouda et al. 2015). The broad class of such proteins has been implicated in intracellular signaling, neuroprotection, and inhibitory processing. The proteins most commonly studied have been parvalbumin (PV), calbindin (CB), and calretinin (CR). A second, calcium-associated protein that is involved in the synthesis of nitric oxide (NO) has also been shown to be expressed in an age-dependent manner. This molecule is nicotinamide adenine dinucleotide phosphate diaphorase (NADPHd) and is believed to function to control calcium buffering and intercellular signaling (Reuss 2000; Gray et al. 2013a). A summary of findings from the rodent can be seen in Fig. 5.2, with arrows showing increases and decreases of the neuronal expression of different molecules from the cochlear nucleus up to the auditory cortex (Fig. 5.2, right side). These differences between increases and decreases depend on the molecule that is being tested, the species (i.e., rat vs. mouse), and even the strain of the particular species (see Ouda et al. 2015).

More recently, similar investigations have been carried out, primarily with PV and NADPHd, in young and aged macaque monkeys (Fig. 5.2, left side). There have been similar findings between the macaque and rodent, but in macaques the results have all been increases in the number of cells expressing these molecules, and no decreases. Increases in PV+ expressing cells have been found in the medial superior olivary (MSO) nucleus (Gray et al. 2014b), in both the central and external nuclei of the inferior colliculus (IC; Engle et al. 2014), and in both the ventral and medial divisions of the medial geniculate nucleus of the thalamus (Gray et al. 2013a). Importantly, these changes appear to be greater in the auditory system compared to the visual system, as the changes in the medial geniculate were greater than those in the lateral geniculate, even for sections on the same histological slide.

For NADPHd, there were increases in neurons expressing this protein in the cochlear nucleus, but only the posterior ventral division (PVCN), and not the anterior ventral division (AVCN) or the dorsal division (DCN; Gray et al. 2014a). The increase in NADPHd expressing cells was also noted in the MSO, as with PV+ cells (Gray et al. 2013b), but there was no change in NADPHd expressing neurons in the

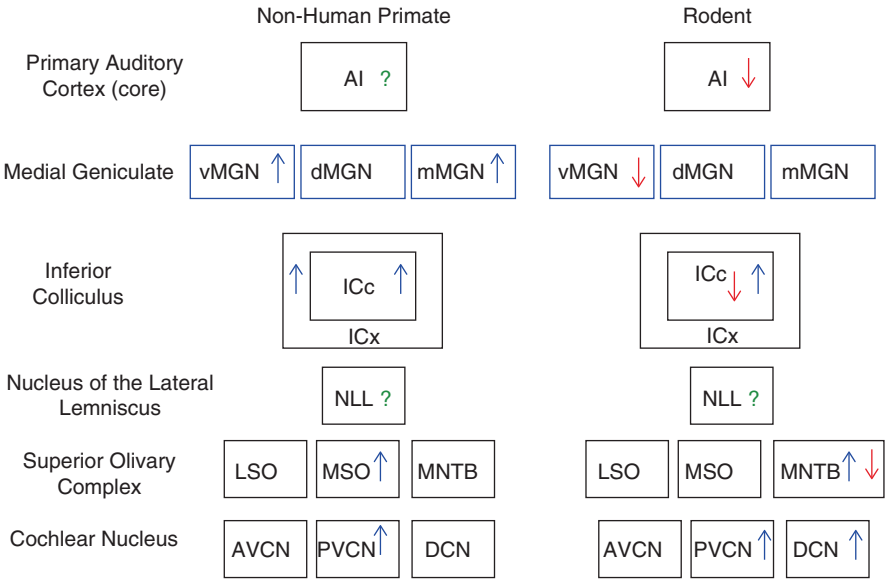

Fig. 5.2 Summary of histological changes of calcium-associated protein expression in neurons in the ascending auditory system in macaque monkeys (left) and rodents (right). Upward blue arrows indicate an increase in the number of calcium-associated protein expressing neurons, downward red arrows indicate a decrease in calcium-associated protein expressing neurons, and green question marks indicate it has not yet been tested. The nonhuman primate data are taken from rhesus macaques, and the rodent data are taken from several strains of mice and rats. A1, auditory cortex; AVCN, anteroventral cochlear nucleus; DCN, dorsal cochlear nucleus; dMGN, dorsal division of the medial geniculate nucleus; ICc, inferior colliculus, central nucleus; ICx, inferior colliculus, cortex; LSO, lateral superior olive; mMGN, medial division of the medial geniculate nucleus; MNTB, medial nucleus of the trapezoid body; MSO, medial superior olive; NLL, nucleus of the lateral lemniscus; PVCN, posterior ventral cochlear nucleus; vMGN, ventral division of the medial geniculate nucleus. (Data taken from Gray and Recanzone 2017)

IC (Engle et al. 2014). This molecule was not tested in the medial geniculate nucleus. Thus, like in rodents, there are changes in the expression of different calcium-associated proteins throughout the ascending auditory system as a function of age in macaque monkeys.

It should be noted, however, that PV+ and CB+ cells are physiologically much more diverse in subcortical areas compared to the cerebral cortex, striatum, and hippocampus. In these forebrain structures, PV+ and CB+ cells are most commonly associated with γ-aminobutyric acid (GABA)ergic transmission (Gray et al. 2014a). However, in subcortical structures of the superior olivary complex and IC, the percentage of PV+ and CB+ neurons that also express GAD67, a marker for GABAergic transmission, is significantly reduced. This observation is consistent with those made in rodents (Fredrich et al. 2009), indicating that these changes in calcium-binding proteins as a function of aging are not a simple proxy for changes in the balance of excitatory and GABAergic inhibitory transmission.

Studies in rodents have also shown that there are changes in the expression of both excitatory and inhibitory receptors and levels of the inhibitory neurotransmitter GABA (see Caspary et al. 2008). This has led to the hypothesis that aging results in an imbalance of excitation and inhibition, and the question is raised whether these changes could underlie the perceptual deficits noted in psychophysical experiments. The cerebral cortex is necessary for both spatial and temporal processing (Heffner and Heffner 1990; Harrington et al. 2001), and the cerebral cortex would necessarily inherit any changes in the subcortical areas, so one important question is whether there are any changes in the neuronal activity of the cerebral cortex that could underlie the age-related deficits in spatial and temporal processing.

5.2.3 Implications of Histochemical Results

Taken together, in both rodents and primates, there are multiple changes in the ascending auditory system as a function of age. Questions that are raised by these neuroanatomical findings are: (1) How are these changes reflected in auditory cortical activity? (2) What is the general consensus of the overall effect of these changes? The results from the periphery indicate that there is an overall decrease in excitatory drive from the cochlea during the aging process. How this is compensated for in the brainstem, midbrain, and thalamus is less clear, although the overall pattern of results is that there is an overall decrease in inhibition, resulting in a change in the excitatory–inhibitory balance in these structures. This would generally result in an increase in activity, either spontaneous, driven, or both (see Walton 2010; Juarez-Salinas et al. 2010). Whether this would also result in a change in the selectivity of the neuronal responses is addressed further in Sect. 5.3.

Finally, these changes noted in calcium-binding proteins (such as PV) and calcium-associated proteins (such as NADPHd) may not be specifically, or completely, related to changes in the excitatory/inhibitory balance, but may be indirectly related to these changes. For example, an increased firing rate will result in increased intracellular calcium, which is potentially very toxic to the cell and is part of the cascade leading to excitotoxicity (see Gray and Recanzone 2017). Similarly, NO has also been implicated in excitotoxicity as well as having a neuroprotective role, and also in the modulation of glutamate function. Thus, the functional implications of different changes of calcium-binding and calcium-associated proteins as a function of age are far from clearly understood and may well turn out to be much more complicated than originally thought.

5.3 Physiological Studies in the Auditory Cortex

The primate auditory cortex is organized in a core, belt, and parabelt fashion (Kaas and Hackett 2000; Rauschecker and Tian 2000; Fig. 5.3). The core is made up of three areas: the primary auditory cortex (A1) most caudally, the rostral area (R), and

the rostrotemporal area (RT) located most rostrally. Each of these areas responds well to tone stimuli and has a complete representation of the cochlea (Merzenich and Brugge 1973; Petkov et al. 2006). This representation forms "isofrequency" bands with best frequency reversals at the border between cortical fields such that high frequencies are represented most caudally in A1, there is a reversal at low frequencies between A1 and R, then again a reversal at high frequencies between R and RT, with the lowest frequencies represented most rostrally in RT (see Fig. 5.3).

Surrounding the core are belt areas that are strongly interconnected to the adjacent core areas (see Kaas and Hackett 2000). These cortical areas respond better to band-passed stimuli, containing more spectral information, compared to the core, which responds better to tonal stimuli (Rauschecker and Tian 2004; Kusmierek and Rauschecker 2009). One area in particular, the caudolateral area (CL), is thought to specialize in spatial processing, whereas the more rostral belt area adjacent to RT, the anterior lateral area (AL), is thought to specialize in nonspatial processing (Rauschecker and Tian 2000; see also Recanzone and Cohen 2010). There is supporting evidence from human imaging studies for parallel processing streams in the auditory cortex, with a caudal stream processing spatial information and a rostral stream processing nonspatial information (Rauschecker 1998; Ahveninen et al. 2013). Evidence from monkey studies largely support this view. For example, in spatial processing the caudal fields, particularly CL, have sharper spatial tuning (Woods et al. 2006). Firing rates from CL neurons provide enough information to accurately localize broadband stimuli in azimuth (Miller and Recanzone 2009) and both broadband and narrow band stimuli in azimuth and elevation (Recanzone et al. 2000). In contrast, it is difficult to quantify what types of nonspatial stimuli the

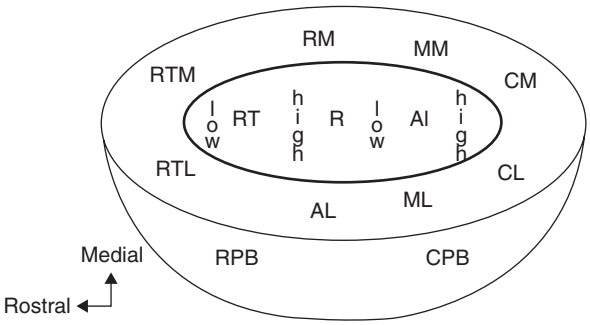

Fig. 5.3 Schematic diagram of the primate auditory cortex. The inner ellipse (bold) represents the core area, made up of three distinct cortical areas from caudal to rostral: primary auditory cortex (A1), rostral area (R), and rostrotemporal area (RT). Surrounding this region is the belt cortex, made up of eight distinct cortical fields: caudomedial area (CM), middle medial area (MM), rostromedial area (RM), medial rostrotemporal area (RTM), lateral rostrotemporal area (RTL), anterolateral area (AL), middle lateral area (ML), and caudolateral area (CL). These areas receive their densest cortico-cortical projections from adjacent cortical areas. The lateral cortex consists of two fields, rostral parabelt (RPB) and caudal parabelt (CPB). As with the belt areas, they receive the bulk of their cortical projections from adjacent fields. Thus, the core is not directly connected to the parabelt. (Adapted from Kaas and Hackett 2000)

anterior pathway would be encoding. While some studies indicate that vocalizations are selectively processed in anterior fields (e.g., Tian et al. 2001; Fukushima et al. 2014), others have shown that they are equally selective for both forward and time-reversed vocalizations (Recanzone 2008). Alternatively, using amplitude-modulated (AM) noise stimuli has shown that there are clear differences in processing between the core area A1 and the medial lateral (ML) belt area (Downer et al. 2017). Differences in physiological methods (local field potential vs. single neuron activity), stimuli (forward and reversed vocalizations vs. forward and synthesized vocalizations), and task demands could all play a role in these differences between studies.

5.3.1 Spontaneous and Driven Activity

With respect to the general activity of auditory cortical neuron in aged animals, the predictions from the neurohistochemical changes were that there should be increased spontaneous and driven firing rates (see Sect. 5.2.3). Alternatively, it could be that higher firing rates, such as those seen in the IC in aged mice (Walton et al. 2002; see Walton 2010) as well as in the medial geniculate of aged rats (Richardson et al. 2013) would be compensated for by the cerebral cortex. Studies in nonhuman primates indicate that both spontaneous and driven activity are increased in aged auditory cortex. Two aged monkeys with normal hearing audiograms were tested using a variety of passively presented broadband noise, tones, and AM noises. The responses of both A1 and CL neurons were then compared to those measured in younger monkeys to the same stimuli. As predicted, the first and most notable difference was in the spontaneous activity, which was much higher in aged compared to younger animals in both A1 and CL (Juarez-Salinas et al. 2010; Ng and Recanzone 2017). This is similar to higher spontaneous rates seen in visual cortex of rhesus monkeys (Schmolesky et al. 2000; Yu et al., 2006; Liang et al. 2010).

For these same aged monkeys, the driven activity was also increased compared to younger animals for broadband noise and sequences of either tone pips or noise bursts. Again, similar studies in visual cortex of monkeys showed an equivalent result. This indicates that the changes in excitatory and inhibitory balance noted in the subcortical structures remains, and perhaps is even exaggerated, in the auditory cortex (Walton et al. 2002; Richardson et al. 2013).

5.3.2 Spatial Processing

Increases in both spontaneous and driven activity do not necessarily indicate that any resolution or specificity of the neural encoding of specific auditory features has been compromised. For example, if the signal-to-noise ratio remains constant then simply changing the gain should have limited effect on the perceptual consequences.

However, given that age-related hearing deficits can manifest as spatial and temporal processing deficits (see Gordon-Salant, Wingfield, and Shader, Chap. 9), and these deficits can be independent of hearing loss as defined by the audiogram, a clear question is whether the specificity of the neuronal responses is also altered, particularly because spatial processing is one of the main deficits in age-related hearing loss, and it had previously been shown that area CL neural activity could account for spatial localization ability.

The two monkeys with normal hearing described above were tested using broadband noise from 16 speakers spanning 360 degrees in azimuth. The spatial tuning across the population of recorded neurons is shown in Fig. 5.4. Here, each cell was normalized so that the best response corresponded to 0 degrees, and locations to the right were assigned positive values and those to the left negative values. The overall activity was set at the best response as 1.0; thus these curves indicate the relative activity across the population as a function of distance from the best location. For young animals, the population response of A1 neurons for all locations was above the spontaneous activity (dashed line) but decreased to about 10% of the best response for locations farthest away (+/− 180 degrees). In contrast, CL neurons showed much greater decreases in activity with greater distance from the best direction, to the point that the population response was inhibited beyond about 90 degrees from the best direction. Thus, it appears that inhibition or suppression carves out the flanks of the spatial receptive fields, making them sharper.

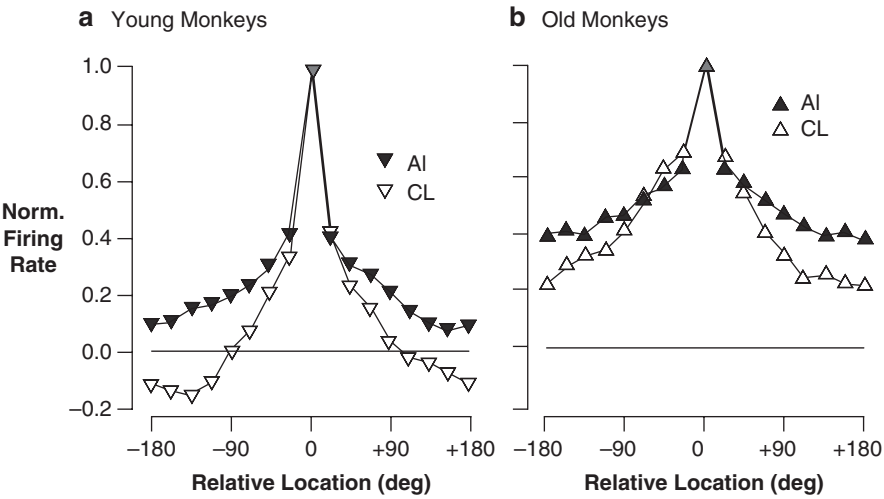

Fig. 5.4 Spatial tuning of the population of primary auditory cortex (A1) and caudolateral area (CL) neurons. (**a**) Normalized firing rates as a function of the location that elicited the greatest response (0 degrees). Filled symbols show the population response of A1 neurons; the open symbols are from CL neurons. The dashed line shows the value corresponding to spontaneous activity. (**b**) Firing rates for old monkeys. Conventions as in **a**. No stimulus locations elicited an inhibitory response (points below the dashed line). There was also a reduced sharpening of spatial tuning between A1 and CL. (Data taken from Juarez-Salinas et al. 2010)

This was not apparent in the population responses in the old monkeys (Fig. 5.4b). In this case, for both A1 and CL, there were no locations that had driven rates below the spontaneous activity. Further, the difference in tuning was much more attenuated, with the CL spatial tuning function not particularly sharper than from the population of A1 neurons. Quantitatively, young CL neurons had the sharpest tuning, and old A1 neurons had the broadest. Interestingly, young A1 and old CL were equivalent in both bandwidth and location.

These data were further examined to determine the timing of the responses (Engle and Recanzone 2012). It was found that in younger animals the first spike latency was greater in CL than in A1, and particularly in CL the latency increased as the stimuli were presented farther away from the best direction. In contrast, in aged animals there was no change in the first spike latency as a function of stimulus location, nor was there a change between CL and A1. Indeed, the first spike latency for all stimulus locations and cortical areas were shorter than those for younger A1 neurons. These results are consistent with observations in the IC of aged mice (Simon et al. 2004).

These results indicate important differences for spatial processing in young and aged animals and support the notion that aged animals have an imbalance of excitatory and inhibitory processing. With decreased inhibition, not only are first spike latencies decreased, but also there is no suppression of activity for locations that are at the flanks of the best direction, preventing the spatial receptive fields from sharpening. This hypothesis remains to be directly tested, however. Some open questions remain at this point, as direct tests of inhibition, or the difference between decreased inhibition versus increased excitation, have yet to be conducted. Intracellular recordings could potentially differentiate between these two possibilities, as could manipulation of excitatory and/or inhibitory neurotransmitters (e.g., Richardson et al. 2013).

5.3.3 Temporal Processing

A key component of complex auditory processing is the ability to accurately encode the temporal envelope of the stimulus. A great deal of information can be gleaned about a stimulus with just this information in the absence of any spatial or spectral information, which can account for the rather remarkable ability for patients to understand speech with a single-channel cochlear implant in the early days of that technology (see Merzenich 2015). One way to model envelope processing is to use AM noise that varies in the modulation frequencies that correspond to the syllabic intervals of speech (Rosen 1992). This stimulus has been used extensively to study the auditory nervous system's ability to encode low-frequency stimulus envelopes (see Joris and Yin 1992; Joris et al. 2004). Responses of A1 cortical neurons using AM noise in these same aged animals were compared to those from younger animals from a different study (Yin et al. 2011; Overton and Recanzone 2016). Both studies investigated the ability of single neurons to encode the envelope of the

stimulus by two different metrics. The first is a firing rate code, where the number of action potentials is compared to spontaneous activity and to each of several different modulation rates. For both studies, a neuron was considered to be sensitive to AM rate if it had a statistically significant response above or below spontaneous activity to at least one AM rate tested. The second metric was a temporal code, where the response to at least one AM rate tested had a statistically significant vector strength (VS) or in a separate analysis, a statistically significant phase-projected vector strength (VSpp), which takes into account low spontaneous activity.

A hallmark symptom of age-related hearing deficits is a reduced ability to understand speech in noise, and this could theoretically be caused by either a reduced number of neurons that can encode the temporal envelope of a sound, how well each neuron is able to encode this information, or some combination of both (Fig. 5.5). When comparing old and young monkeys, the percentage of neurons with significant changes in activity as a function of the rate of these AM stimuli was the same; i.e., it was not the case that there were fewer cells in aged animals that could encode the envelope of the stimulus. However, there was a statistically significant difference in the ways that young and aged neurons encoded these stimuli. In the aged animals, there was an increase in neurons that were sensitive based on the firing rate only, at the expense of neurons that were sensitive both by their firing rate and by their VSpp (but not VSpp only). Thus, in aged animals there was a fundamental change in the neural encoding strategy from neurons that used both types of codes to those that used only the firing rate code. What is not clear from this analysis is why that may be, but it does suggest that it could be a compensatory mechanism to account for weaker temporal processing ability.

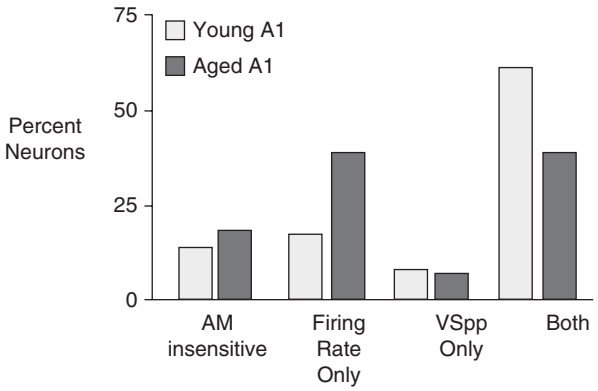

Fig. 5.5 Distribution of neurons encoding amplitude-modulated (AM) stimuli. A small percentage of recorded neurons did not have a statistically significant response to any of the AM stimuli based on either firing rate or phase-projected vector strength (VSpp, far left). The percentage of neurons that showed statistically significant responses to any of the AM stimuli presented by firing rate only (second from left), or VSpp only (second from right), or both (far right) are shown for young (open) and old (gray) neurons. A1, primary auditory cortex

To test this possibility, the VSpp was compared between aged and younger neurons. Across the population of cells, there was a significant decrease in VSpp across lower modulation frequencies tested (4–32 Hz) in the aged neurons compared to the younger neurons. These differences were lost at higher AM rates, generally as both sets of neurons had relatively low VSpp values. The firing rates across the population of neurons were relatively flat as a function of AM rate. Interestingly, while the relative firing rates (driven/spontaneous) were equivalent between young and old neurons for those cells that had significant responses using both temporal and rate metrics, those neurons that were only sensitive by the firing rates had more than two times greater firing rates relative to the responses in old compared to young neurons. Finally, the difference between the best modulation frequency using the firing rate code was compared to the best modulation frequency using the temporal code for those neurons that were significant for both metrics. In young animals, these two values were well correlated, whereas in older animals no such correlation existed. This could be accounted for primarily because the modulation transfer functions for firing rate coding in aged neurons were generally nonmonotonic, with the highest firing rate at the highest modulation frequency tested, as opposed to specifically tuned to some lower modulation frequency.

These data in alert primate auditory cortex are similar to those seen in rodent subcortical areas (e.g., Walton et al. 2002; Walton 2010). Higher firing rates do not necessarily mean better performance, and in this case there is worse temporal fidelity across both individual neurons and across the population. This would explain a motivation for shifting between a dual temporal and rate coding of sound envelopes to a simple rate code, given the temporal code had a greater deficit. It is not clear if this strategy is adequate to maintain the ability to process this temporal information, or if this shift necessarily leads to the perceptual deficits that are observed in humans with age-related hearing deficits.

In addition to broad changes in the speech envelope that are generally at the syllabic level (see Rosen 1992), many components of speech also have abrupt onsets and offset corresponding to stop-consonants and other utterances. To test the ability of aged and young neurons to encode these more rapid transients, a series of tone and noise pips were presented to these same monkeys (Ng and Recanzone 2017). This study was consistent with those described above, with shorter latencies in aged neurons, minimal differences between A1 and CL encoding, and better temporal resolution in young animals compared to aged animals. In addition, analysis of the similarity of the responses to different stimuli showed that the responses of aged neurons were more similar between the different stimuli compared to the responses of young neurons. As a consequence of this, younger neurons were much better able to discriminate between the different stimuli compared to aged neurons. This is exactly as predicted to account for speech unintelligibility, i.e., a difficulty in discriminating between different phonemes.

These two studies, using temporally complex stimuli, converge on the notion that aging causes temporal processing differences in aged neurons compared to younger neurons. Thus, throughout the life of an animal, the processing abilities of their cortical neurons is altered, going from a more temporally based code to a more

firing rate code. Further, the transformations between core and belt cortical regions are diminished in aged neurons. These two differences could clearly underlie changes in the ability to understand complex acoustic stimuli.

The results of these physiological experiments indicate that there are dramatic changes in the way that cortical neurons process acoustic stimuli in aged animals compared to younger animals, even though the aged animals have normal tone and noise detection thresholds. These differences are consistent with an imbalance of the normal excitatory and inhibitory processes. Across both core and belt cortical areas, there was an increase in both spontaneous and driven responses, as well as a decrease in first spike latency. These changes can also account for the broader spatial tuning in aged animals, as there is limited inhibition of the flanking spatial locations that allow this sharpening. It also can account for the reduced temporal responses for both AM noise stimuli as well as tone and noise burst sequences. Finally, the differences that are easily noted between core and belt areas in young animals are virtually absent in aged animals. This indicates that there is a disconnect in the normal cortical hierarchical processing. How extensive this disconnect is, either between other core and belt areas, or between belt and higher order cortical areas, or even in different sensory modalities, remains to be investigated.

5.4 Summary

Normal aging is hypothesized to result in an alteration of the excitatory and inhibitory balance as a consequence of a decreased afferent drive from the cochlea. This can occur in the absence of any audiometric deficits, yet still result in age-related hearing deficits (Fig. 5.6). This chapter reviews both anatomical and physiological evidence from a nonhuman primate model of age-related hearing loss, the macaque monkey. Anatomical studies conducted across subcortical areas are consistent with the larger body of rodent work in that there are clear changes in the numbers of neurons that express different calcium-binding and calcium-associated proteins. Electrophysiological recordings in young and aged monkeys in both the core and belt of auditory cortex show changes that are consistent with both spatial and temporal processing deficits seen in humans with age-related hearing deficits. Spatial receptive fields are broader in aged animals compared to younger animals, and there is not a sharpening of spatial tuning between core and belt areas. For temporal processing, while the proportion of neurons that are sensitive to the envelope of different sounds is the same between young and old animals, the ability to encode the envelope is reduced. This results in the neurons relying more on a firing rate code compared to a temporal code, and the ability to discriminate between different stimuli using this code is reduced in old monkeys compared to young monkeys. All of these results, including the overall higher spontaneous and driven firing rates and reduced latencies, are consistent with an imbalance of the excitatory and inhibitory circuits that are initiated early in the auditory pathway and are inherited, and likely exacerbated, at the cortical level. The factors are all consistent with a reduced ability

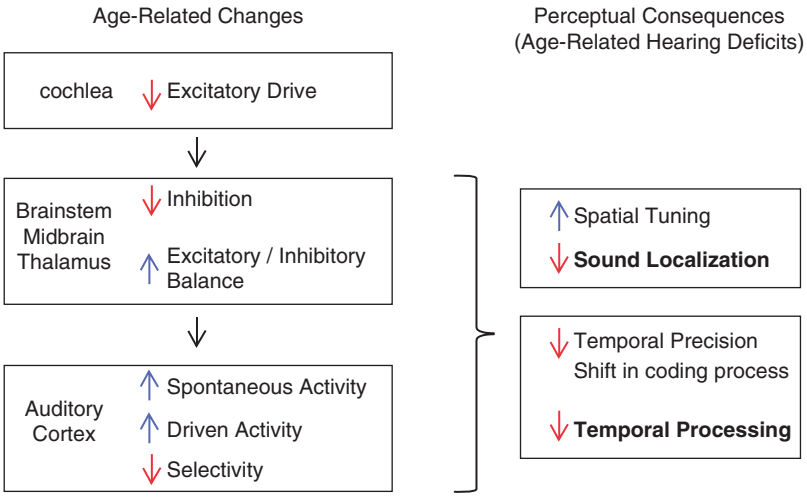

Fig. 5.6 Summary of the age-related effects on auditory processing. The left side shows the changes in the periphery and subcortical structures resulting in physiological changes in the auditory cortex. The right side shows the perceptual consequences of these changes, which could account for the two main age-related hearing deficits: sound location processing and temporal processing

to process spatial and temporal acoustic events and could underlie the age-related hearing deficits that are common with normal aging.

These data in a nonhuman primate model are largely consistent with the more numerous studies in rodent models, but several key questions remain. Perhaps the most germane are: (1) At what level(s) in the ascending auditory axis do these changes occur, and which of these would be most amenable to interventions? (2) Where does the change in inhibition occur, i.e., which type(s) of inhibitory neurons are most affected? (3) Is it possible to prevent or even reverse these effects? Unfortunately, there is little information with regard to the first question, as the ascending auditory system in the alert primate is extremely difficult to study. This is primarily due to the large size of the cranium and the overlying musculature, which makes targeting subcortical structures problematic using the same techniques developed for cortical recordings. The IC has been targeted in younger animals (Pages et al. 2016; Caruso et al. 2018), but little effort has been made to investigate the medial geniculate nucleus of the thalamus (Hocherman and Yirmiya 1990; Selezneva et al. 2017). It is likely therefore that the field will be dependent on the rodent models for subcortical investigations, particularly in the brainstem.

With respect to the type(s) of inhibitory neurons that are affected, studies have indicated that somatostatin-expressing neurons in the cerebral cortex could be primary candidates in rodent models (de Villers-Sidani et al. 2010; Voss et al. 2016), although this has not yet been investigated in primates. If one were able to specifically target such neurons, either early in the aging process and more aggressively once age-related perceptual deficits are noticed, these deficits may be effectively treated.

Finally, there is also good evidence that these age-related changes can be reversed, both in rodent models (de Villers-Sidani et al. 2010; Voss et al. 2016) as well as human subjects (White-Schwoch et al. 2013; Cheng et al. 2017) through specifically targeted acoustic training paradigms. The animal studies also show that the histochemical changes seen in cortex are also reversed in parallel with the changes in perception. Primate models may be able to advance these studies even further given the greater behavioral repertoire of macaque monkeys. This would allow the ability to determine which training paradigms are best able to transfer across different acoustic parameters, and how the underlying excitatory/inhibitory balance is improved or restored by these paradigms.

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Chapter 6
The Aging Auditory System: Electrophysiology

K. C. Harris

Abstract Aging results in a complex pattern of changes from the cochlea to the cortex. Through the use of neuroimaging techniques, including electrophysiology (EEG), effects of age on neural structure and function have been identified at the level of the auditory nerve, midbrain, and auditory cortex. This chapter takes a systems approach and describes results from electrophysiologic studies of the aging auditory system and focuses on the effects of age, experience, and disease.

Keywords Aging · Auditory brainstem responses · Compound action potentials · Cortical evoked potentials · Electrophysiology · Envelope following responses · Frequency following responses · Plasticity

6.1 Introduction

Human presbycusis, or age-related hearing loss, is typically defined by age-related deficits in the peripheral auditory system (cochlea) and associated hearing loss characterized by elevated pure-tone thresholds. However, the notion that more central auditory deficits contribute to human presbycusis has gained acceptance. In fact, evidence has accumulated in support of an age-related multifactorial central component of presbycusis that results in a complex pattern of changes throughout the auditory system, from the auditory nerve to the cortex. Age-related changes can occur independently at each level of the system, changes at the periphery may result in apparent changes at more central levels, and complex interactions can occur across the system. Further complicating this, the precise changes contributing to age-related deficits are difficult to characterize, particularly when using behavioral

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methods that may be affected by changes at each level of the auditory system, in addition to possible cognitive influences. Moreover, because of the complexity of central presbycusis, the mechanisms that are the best targets for interventional strategies or their locations are not always apparent. One solution is the use of neuroimaging methods, including electrophysiology, which can better define the roles of neural systems that underlie aging and the central auditory system. In laboratory animals, these include both noninvasive and invasive measures of neural activity as described in Syka, Chap. 4 and Recanzone, Chap. 5. In human subjects, neural activity can be measured indirectly using electroencephalography/magnetoencephalography (EEG/MEG; a full list of abbreviations used in this chapter is provided in Table 6.1) and functional magnetic resonance imaging (fMRI) (see Kuchinsky and Vaden, Chap. 10). In combination with behavioral measures, these techniques can identify specific locations or potential mechanisms in the auditory system that may contribute to age-related deficits.

EEG and fMRI methodologies each have benefits and limitations, and the choice of the optimal method is dependent on the specific research question. A benefit of both techniques, but particularly EEG, is that laboratory animals and humans can be assessed using very similar experimental paradigms. Although results from humans can better characterize the functional relevance of observed changes in neural function when combined with behavioral measures, in vivo studies with animals can better identify important genetic, circuit, and histopathologic changes that underlie age-related deficits in auditory processing when a specific pathology is known or induced. A better understanding of the linkages between results from human behavioral and neuroimaging studies with results from animal EEG studies is also important for assessing and validating potential intervention strategies designed to prevent, reverse, or delay the onset and progression of age-related hearing loss.

Table 6.1 Abbreviations used in this chapter

ABR	auditory brainstem response
BOLD	blood-oxygen level dependent
cABR	complex ABR
CAEPs	cortical auditory evoked responses
CAP	compound action potential
EEG	electroencephalography
EFR	envelope following response
FFR	frequency following response
fMRI	functional magnetic resonance imaging
MCI	mild cognitive impairment
MEG	magnetoencephalography
NIRS	near-infrared spectroscopy
PET	positron emission tomography
PLV	phase-locking values
SNR	signal-to-noise ratio

An advantage of EEG over fMRI is the precise temporal resolution of EEG, with EEG capable of characterizing neural activity on a millisecond scale and capturing neural synchrony across trials. This apparent difference in temporal resolution is a consequence of the differences in how EEG and fMRI measure neural activity. EEG directly measures the electrical properties of cells or tissues, or changes in these properties, typically measured as a voltage change, in response to a stimulus. When neuron(s) are stimulated, a hyperpolarization or depolarization occurs, and once the resulting membrane potential reaches a certain threshold, an action potential can be recorded as a change in electrical activity. In humans, these recordings are far-field (typically from scalp or ear canal electrodes), or distant from the generator of the potential, and reflect the summed average of the potentials from large groups of neurons firing synchronously. In contrast, fMRI indirectly measures neural activity by assessing differences in blood-oxygen level dependent (BOLD) contrast between two conditions, or the hemodynamic response, and is based on the assumption that cerebral blood flow and neural activity are coupled (Logothetis and Wandell 2004). This dependence on blood flow essentially works like a low-pass filter, reducing the temporal resolution of the response to hundreds of milliseconds or seconds. Yet, spatial resolution is much better in fMRI compared to EEG, as fMRI reflects neural activity by examining changes in blood flow in the local vasculature, resulting in a corresponding local reduction in deoxyhemoglobin, which is itself paramagnetic and serves as the source for the signal for the fMRI (see Kuchinsky and Vaden, Chap. 10).

As described in Ohlemiller and Spankovich, Chap. 3; Syka, Chap. 4; and Recanzone, Chap. 5, animal models provide strong evidence for effects of aging on auditory processing at each level of the auditory system. Whereas fMRI has better spatial resolution for identifying changes at the level of the cortex, EEG is the only method capable of assessing changes in neural function throughout the auditory system, at the level of the auditory nerve, brainstem, and cortex (Fig. 6.1). This chapter focuses on the use of EEG to characterize age-related changes in the central nervous system, in older adults with and without hearing loss. A concise yet accurate way to characterize age-related changes in the central auditory system is to segregate auditory physiology into structurally based components consisting of the auditory nerve, brainstem, and cortex.

Using EEG, auditory nerve, brainstem, and cortical activity can be differentiated by time (latency of responses) and frequency (far-field phase-locked activity). Auditory nerve activity occurs earliest and can sustain synchronized activity to much higher frequencies than cortical activity. Cortical activity can be further localized to general cortical structures and regions through the use of source reconstruction techniques. Frequency patterns of activity at the level of the cortex change with subject state and cognitive processing, and therefore cortical activity is often further filtered into relatively lower frequency bands that represent differences in activity across cortical networks, as described later (Sect. 6.3). Although this chapter takes a systems approach in describing EEG activity, keep in mind that activity measured from higher auditory levels is only as good as the fidelity of the signal it receives from more peripheral locations. This chapter focuses on afferent activity from the auditory nerve to the cortex; the complex efferent system is beyond the scope of the chapter.

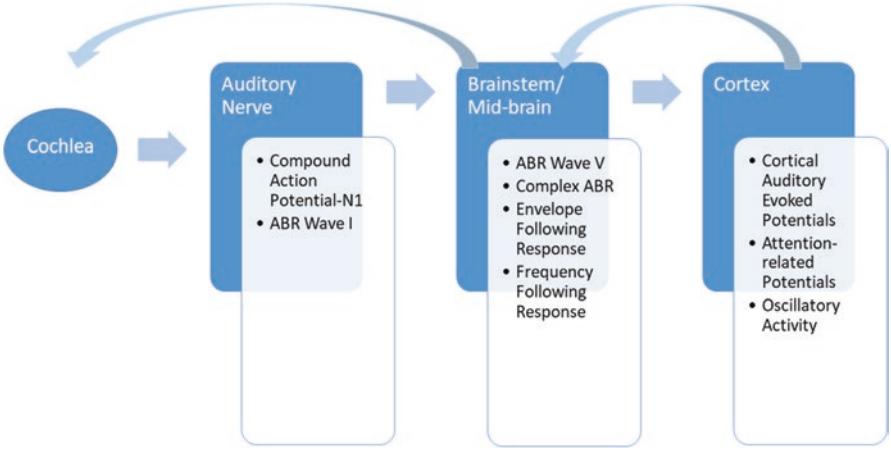

Fig. 6.1 Schematic overview of electroencephalography (EEG) of the central auditory system, including measures of the auditory nerve, brainstem/midbrain, and cortex. The responses occur sequentially in time, as depicted from left to right, as activity ascends the auditory system. Although beyond the scope of this chapter, the efferent pathways are depicted by arrows moving from right to left, which also affect EEG and behavioral measures

The precise temporal resolution of EEG is of particular importance in studies of age-related hearing loss, as deficits in temporal processing have been identified as a possible contributor to deficits in speech recognition by older adults (see Gordon-Salant et al., Chap. 9). The precise temporal resolution of EEG provides a means to examine the effects of reduced temporal processing on the use of temporal cues in speech (such as differences in voice-onset time) or in nonspeech stimuli, such as the onset and offset of a silent gap in a broadband noise.

6.2 Auditory Nerve

Degeneration of the auditory nerve was one of the four subtypes of presbycusis originally described by Schuknecht (Schuknecht and Gacek 1993). In its original description, auditory nerve degeneration was thought to occur secondary to hair cell loss (Bohne and Harding 2000). More recent evidence suggests that neural degeneration may occur independently of and precede hair cell loss ("primary neural degeneration"; Hao et al. 2014; Wu et al. 2018). Identifying the underlying mechanisms responsible for age-related neural degeneration is critical because the auditory nerve represents the sole route from the inner ear to the central auditory system. Acoustic information is encoded by differences in the spike timing and rates across auditory nerve fibers. The redundancy of afferent information coded in auditory nerve fibers means that a loss of as much as 80% of auditory nerve synapses can occur without affecting detection of pure-tone signals (Schuknecht and Woellner 1953; Lobarinas et al. 2013). However, loss of these fibers is thought to contribute

to an under-sampling of the auditory signal (Lopez-Poveda and Barrios 2013), among other effects. While this undersampling would not affect detection thresholds, it may impact neural encoding for higher level or rapid onset signals, particularly in complex listening environments when decoding is dependent on the resolution of the auditory system, such as segregating a speech signal in the presence of background noise.

The audiogram's insensitivity to auditory nerve synaptopathy, coupled with morphologic findings of auditory nerve loss, led to a resurgence in research aimed at characterizing human auditory nerve function. In humans, the only noninvasive neuroimaging method currently capable of measuring auditory nerve function is EEG, specifically, the compound action potential (CAP) or wave I of the auditory brainstem response (ABR). These extracellular potentials provide a relatively gross representation of the summed response of a population of auditory nerve fibers. Thresholds for these *summed responses* reflect cochlear damage but are less sensitive to partial neural degeneration. However, CAP/ABR wave I responses to signals at suprathreshold levels may provide novel information pertaining to auditory nerve function and integrity, including neural degeneration. A partial loss or dysfunction of auditory nerve fibers in animal models with increasing age has been associated with a reduction in maximum amplitude and shallower slopes of amplitude input–output functions, consistent with fewer responding fibers and/or reduced synchronous activity (Hellstrom and Schmiedt 1990; Mills and Schmiedt 2004). Cross-sectional data from older adults suggest a similar phenomenon, with older adults showing shallower input–output slopes of wave I and reduced maximum amplitudes compared to younger adults (Konrad-Martin et al. 2012; McClaskey et al. 2018) (Fig. 6.2).

One confounding factor in determining how age affects auditory nerve function is the strong correlation of age and audiometric thresholds, which is often addressed by comparing response amplitudes from younger and older adults with normal hearing. Burkard and Sims (2001) and McClaskey et al. (2018) used that approach and found significantly smaller auditory nerve response amplitudes in older compared to younger adults with normal hearing, suggesting a reduction in the maximum amplitude of the CAP wave I with advancing age, independent of threshold elevation. Similar reductions in ABR wave I amplitude have been reported in a large cohort of predominantly male veterans aged 26 to 71 with a wide range of hearing thresholds, where increased age substantially reduced amplitudes of ABR wave I largely independently of hearing threshold differences (Konrad-Martin et al. 2012).

It has been widely hypothesized that deficits in auditory nerve function may lead to deficits in auditory processing and poorer speech recognition in challenging listening conditions (Marmel et al. 2015; Bramhall et al. 2018; Harris et al. 2018). However, the association between changes in auditory nerve responses, measured with the CAP or ABR wave I, and declines in speech recognition is still not resolved. In a relatively large cohort of subjects ($N = 57$), Bramhall et al. (2018) reported that wave I amplitudes decreased with increasing age, and that decreased wave I amplitudes and hearing loss were associated with poorer speech recognition in noise. In contrast, studies limited to younger and middle-aged adults have largely failed to

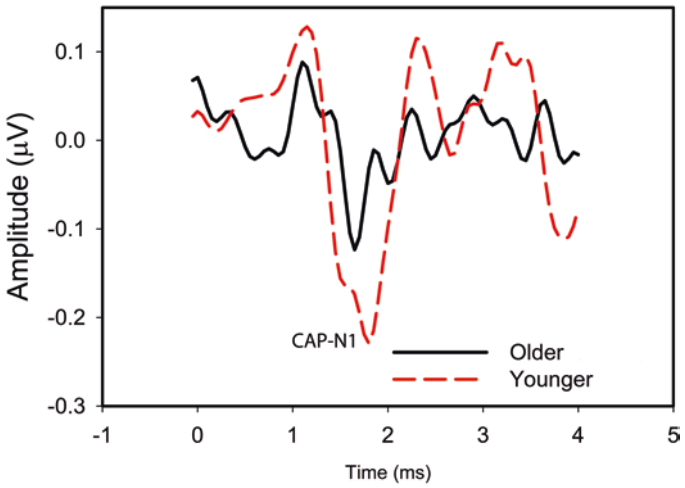

Fig. 6.2 Click-evoked auditory nerve responses of older (solid black line, $N = 38$) and younger (dashed red line, $N = 27$) adults with normal hearing. Older adults, even those with preserved hearing thresholds, show reduced N1 amplitudes of the compound action potential (CAP) response and auditory brainstem response (ABR) wave I (data not shown) at higher stimulus levels compared to those of younger adults. (Data replotted from McClaskey et al. 2018)

find an association between wave I amplitudes and speech-in-noise recognition (Guest et al. 2018). Inconsistencies across studies may reflect the influence of older age in the Brahmhall study or may stem from differences among EEG variables and experimental stimuli, which are most often peak amplitudes in response to click stimuli. Individual differences in peak amplitudes may arise from several factors that vary with age, including nerve fiber loss and dyssynchrony. Both a loss of auditory nerve fibers and deficits in neural synchrony would result in smaller averaged peak amplitudes (Harris et al. 2018). However, it remains uncertain how these metrics may change with advancing age.

New techniques to further characterize auditory nerve function, either through various stimulus manipulations (Kennedy et al. 2017) or by more complex analyses that better assess potential deficits (Harris et al. 2018), may reveal associations between auditory nerve function and behavior. Moreover, in animal models, a loss or inactivity of auditory nerve fibers can lead to compensatory changes throughout the auditory system that restore the gain of the signal but not its temporal fidelity and may disrupt suprathreshold auditory processes (Chambers et al. 2016). Because accurate speech processing depends on activity at the cortical level, these compensatory changes may contribute to some of the discrepancies across studies. Longitudinal studies of changes in speech recognition and wave I amplitudes or studies assessing both auditory nerve and cortical responses are needed to identify the extent to which age-related deficits in auditory nerve function may contribute to speech recognition in noise.

In summary, even after accounting for the effects of hearing loss, aging results in robust deficits in suprathreshold function of the auditory nerve, consistent with the

loss of auditory nerve fibers observed postmortem in aged humans (Makary et al. 2011; Hao et al. 2014). Less certain is the impact of these changes on suprathreshold processing and speech recognition, or the interaction of these changes with environmental factors such as noise exposure (Kujawa and Liberman 2015). Additional studies, particularly longitudinal studies, are needed to provide a more definitive answer to these important research questions.

6.3 Subcortical: Auditory Brainstem and Midbrain

Auditory signals ascending from the auditory nerve are processed by an array of subcortical nuclei that perform a variety of sound processing functions (Carney et al. 2015) and relay information to the cortex. In humans, the primary method of measuring activity from subcortical neurons is EEG, specifically waves III–V of the ABR. Unlike auditory nerve responses, which have been recorded in response to simple transient stimuli such as clicks and tone-bursts, brainstem and midbrain activity has been examined in response to both simple stimuli and more complex and sustained stimuli, including speech, modulated tones, or noise. The use of a variety of simple and complex stimuli has allowed for a more thorough characterization of age-related changes in the function of the auditory brainstem and midbrain, including age-related changes in temporal processing. EEG measures from the brainstem have been used extensively in both the clinic and in research to study the aging auditory system (Konrad-Martin et al. 2012). This is largely because these brainstem responses are less susceptible to effects of attention and can be easily compared with results from animal models, where wave V of the ABR is commonly measured (Mehraei et al. 2016). Moreover, as described in Sect. 6.3.1, changes in these metrics may explain, in part, poorer understanding of speech in noise and music perception in older adults, can be altered by experience such as training or the use of amplification, and may be indicative of disease processes common in aging, such as dementia.

6.3.1 Wave V of the Auditory Brainstem Response

Among brainstem EEG measures, the standard click-evoked ABR has been the most extensively studied. The ABR waveform consists of up to seven peaks that occur within the first 10 ms following stimulus onset. The most studied waves are wave I, originating from the auditory nerve, and wave V, arising from the termination of the lateral lemniscal tract within the inferior colliculus (Hashimoto et al. 1981). In general, ABR wave V amplitudes decrease with increasing age or show no change (Debruyne 1986; Schoof and Rosen 2016). Contributing to the variability across studies, wave V amplitudes are often confounded by the effects of hearing loss and nonpathologic influences such as head size and sex. Despite these con-

founds, age-related decreases in wave V amplitude with increasing age have been observed in subjects with relatively preserved hearing (Burkard and Sims 2001) and in subjects of predominantly one sex (Maurizi et al. 1982; Konrad-Martin et al. 2012). However, all of the studies to date have used cross-sectional designs. Longitudinal studies are needed to better characterize the effects of age on brainstem-evoked responses that occur independently of hearing loss and sex.

Associations between metrics of the ABR may identify not only the source of age-related changes, but also may describe how deficits are propagated throughout the auditory system and may help explain individual differences in auditory function. The amplitude of wave I shows more pronounced effects of age than wave V, with larger amplitude differences between younger and older adults observed for wave I than wave V (Burkard and Sims 2001; Konrad-Martin et al. 2012). This amplitude difference between ABR waves has been interpreted as evidence for central gain (Bramhall et al. 2018; Valderrama et al. 2018), where neural activity at more central auditory structures is maintained at suprathreshold levels despite a reduced output from the cochlear or auditory nerve (Yang et al. 2011; Auerbach et al. 2014). This is consistent with known changes in excitatory and inhibitory transmission in the auditory brainstem of rodents (Milbrandt et al. 1996). The impact of this "central gain" mechanism on auditory processing is not well understood in humans. Despite gain being restored, the temporal fidelity of the signal is still diminished. Moreover, although inconsistencies exist across studies, results from several studies have suggested larger wave V amplitudes in the presence of a diminished wave I may be biomarker for the presence of tinnitus (Kehrle et al. 2008; Milloy et al. 2017).

Several stimulus parameters have robust effects on the ABR, including stimulus presentation rate and intensity level. Examining how these stimulus parameters interact with age to affect the ABR may reveal underlying changes in neural function and help characterize age-related deficits. For example, increasing the stimulus rate has been used as a means to assess neural synchrony, with increasing stimulation rate resulting in smaller amplitudes and longer interpeak latencies between wave I and wave V. However, little is understood about the interaction between age and stimulation rate (Debruyne 1986; Konrad-Martin et al. 2012). Although strong evidence is accumulating in support of age-related changes in the brainstem, the inconsistencies across studies and the known impact of nonpathologic factors, including head size and sex, support the need for large-scale analysis to further characterize the effects of age, and the extent to which changes in the ABR may relate to speech recognition or tinnitus.

6.3.2 Brainstem Potentials as Metrics of Temporal Processing

In addition to the traditional click or tone-burst ABR, brainstem potentials can be recorded in response to more behaviorally relevant stimuli, including speech, music, and complex tones. In response to these more complex stimuli, the brainstem response reflects the temporal discharge pattern of the auditory system up to the

level of the midbrain and consists of a transition period to the onset of the signal and a sustained portion. This response is often termed the frequency following response (FFR), the envelope following response (EFR), or the complex ABR (cABR). For simplicity, this chapter uses the term FFR, which is often used to encompass FFR, EFR, and cABR, and responses to lower frequency fine structure. The FFR closely resembles a low-pass filtered version of the eliciting signal. The fidelity of the EEG response to the eliciting stimuli permits a more in-depth evaluation of several aspects of subcortical encoding. An FFR elicited in response to an 80-Hz amplitude-modulated 3-kHz pure-tone is provided in Fig. 6.3. The 80-Hz modulation is clearly present in the sustained portion of the response.

Analyses of these complex FFR waveforms is typically performed in both the time and frequency domains and includes traditional measures of peak latency and amplitude as well as measures of phase locking, or the consistency of the response across trials. Moreover, the similarity of the FFR to aspects of the eliciting stimulus allows for comparison of timing and phase of the FFR to the stimulus (stimulus-to-response correlations) and across conditions (response-to-response correlations). Taken together, the FFR provides objective measures of subcortical temporal processing that may decline with age and contribute to differences in speech recognition in older adults. Age-related deficits in temporal processing are evident in phase locking, amplitude, stimulus-to-response correlations, and response-to-response correlations of the FFR when elicited to static and sweeping tones, particularly at higher modulation frequencies (Grose and Mamo 2012; Clinard and Tremblay 2013; Marmel et al. 2013). Age-related decreases in response amplitude and phase locking are attributed to neural dyssynchrony, while poorer cross-correlation coefficients suggest a less accurate representation of the stimulus. Additional support for age-related dyssynchrony comes from work by Mamo et al. (2016), in which stimulus jitter was used to model age-related changes in neural synchrony in younger adults. As jitter was increased, the responses of younger adults more closely resem-

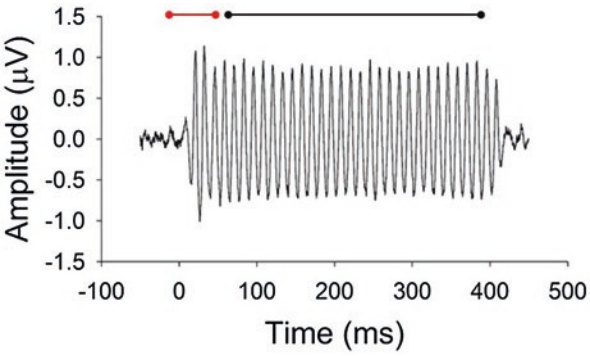

Fig. 6.3 FFR elicited by an 80-Hz amplitude-modulated 3000-Hz tone. The transient portion of the response (red bar) is elicited by the onset of the stimulus. The sustained portion (black bar) closely resembles the envelope of the eliciting stimulus, in this case the 80-Hz modulation. (Data replotted from McClaskey et al. in press)

bled those of older adults. In addition to changes in neural synchrony, age-related changes in the FFR are hypothesized to result from increased "neural noise" that reduces the signal-to-noise ratio (SNR) of the response (Salthouse and Lichty 1985; Bidelman et al. 2014). However, a study by Schoof and Rosen (2016) showed no increase in neural noise with age and instead suggested that a loss in signal amplitude leads to reduced SNR.

Several researchers have examined the effects of age on the FFR in response to speech stimuli, either consonant–vowel syllables like /da/, or to vowels in isolation like /a/. Older adults, even those with normal hearing, have poorer subcortical speech representations than younger adults (Anderson et al. 2013a; Schoof and Rosen 2016). To determine which neural representations are most affected by age, the FFR has been broken down into onset, offset, and sustained portions. While several studies have found effects of age only for peaks at the onset and offset of a response and not the sustained portion of the response in the time domain (Vander Werff and Burns 2011; Clinard and Tremblay 2013), additional measures such as response-to-response correlation coefficients and phase-locking values (PLV) show effects of age both in the transition and steady-state portions of the response (Anderson et al. 2012; Schoof and Rosen 2016).

A goal of many of these studies is to determine the extent to which differences in subcortical encoding predict declines in speech recognition with increasing age. Measures derived from the FFR have been hypothesized to relate to speech recognition in noise, primarily the robustness of fundamental frequency (F0) encoding. Consistent with this hypothesis, some groups have reported that decreased subcortical robustness of F0 is associated with poorer speech recognition in noise (Anderson et al. 2012; Presacco et al. 2016; Schoof and Rosen 2016). In contrast, despite robust changes in the FFR with age, Schoof and Rosen (2016) reported no association with speech recognition in noise. Differences across studies were attributed to the types of background maskers and stimuli employed. Age-related deficits in the subcortical encoding of a variety of cues important for speech understanding are well established (Clinard and Tremblay 2013; Clinard and Cotter 2015). Overall, age-related changes in the FFR seem to represent a robust change in the fidelity and neural representation of auditory stimuli at the level of the brainstem.

6.3.3 Environmental Enrichment: Brainstem Responses

Environmental enrichment, either through musicianship, language learning, or training, is associated with changes in brainstem function and enhanced speech recognition skills. In addition, studies have examined the extent to which this enrichment may ameliorate the effects of aging, or whether similar changes occur through training or amplification later in life. Musicianship often serves as the paradigmatic model for environmental enrichment. Brainstem encoding, as evidenced by the robustness of the FFR, is preserved in musicians, even in the presence of hearing loss (Parbery-Clark et al. 2013) or advanced age (Bidelman and Alain 2015) and may serve to bolster speech recognition with increasing age. Remarkably, these

subcortical enhancements are observed even in older individuals with a moderate degree of training early in life, long after training has stopped (White-Schwoch et al. 2013). This preservation of subcortical processing is thought to arise from the corticofugal system, in which efferent connections between the cortex and brainstem drive this neuroplastic enhancement (Wong et al. 2007). Similar processes may underlie enhanced subcortical processing in multilingual adults (Intartaglia et al. 2017). Remarkably, there is growing evidence that even relatively short periods of musical training may lead to reversals in age-related deficits in subcortical encoding and improve auditory perception (Anderson et al. 2013b). These authors hypothesized that activity-driven increases in inhibitory neurotransmittors may contribute to the enhancement in subcortical encoding. Environmental enrichment in older adults with hearing loss may also occur through the restoration of audibility by amplification. However, at this time, only limited evidence exists to suggest that use of hearing aids may offset subcortical neural timing delays and improve encoding of F0 (Karawani et al. 2018). Taken together, studies of the FFR and aging support the hypothesis that aging's detrimental effect on temporal processing results from poorer auditory encoding before or at the level of midbrain, but these may be ameliorated, in part, through environmental enrichment and neuroplastic mechanisms.

6.3.4 Associations with Cognitive Decline: Brainstem Responses

As described later in Sect. 6.4.4, hearing loss is associated with mild cognitive impairment (MCI) and dementia and may contribute to complex changes in brain structure and function at the cortical level. However, an EEG study by Bidelman et al. (2017) suggests that the pathophysiology of cognitive impairment may arise earlier in the auditory system, and the FFR may serve as a potential biomarker for MCI. When compared to age-matched controls, they observed distinctive changes in the MCI experimental group versus controls, and distorted connections between the brainstem and cortex (Bidelman et al. 2017). An earlier study suggested a similar brainstem effect and reported that, although transient responses such as wave V were normal in cognitively impaired individuals, a slow wave brainstem component was increased in impaired individuals compared to controls (Irimajiri et al. 2005). Although additional studies are needed to explore these relationships, these findings suggest that the pathophysiology associated with age-related cognitive decline may be evident in early sensory processing, mere milliseconds following sound onsets.

6.4 Auditory Cortex

EEG at the level of auditory cortex represents the culmination of the afferent pathway and communication with other cortical brain regions. Owing to this complexity, age-related changes observed in the EEG may arise from differences in the

periphery, auditory cortex, nonauditory regions such as those that control attention, or any combination. Similar to lower levels of the auditory system, cortical EEG can be analyzed in either the time or frequency domain depending on the research question. Moreover, patterns of activity between and across electrodes can be analyzed to approximate where in the brain deficits occur and identify changes in how brain areas interact. This section focuses on (1) effects of age on cortical auditory evoked responses (CAEPs), mainly the P1–N1–P2 complex, and auditory neural oscillations, and (2) the extent to which these cortical changes are associated with temporal processing and speech recognition, are affected by attention and experience, and are predictive of cognitive decline.

6.4.1 Associations with Temporal Processing: Cortical Responses

Long-latency CAEPs are an objective, noninvasive index of neural activity related to sensory, perceptual, and cognitive processes. The P1–N1–P2 complex occurs before 200 ms after stimulus onset, is an obligatory response to the physical characteristic of the eliciting stimulus, and is thought to signal neural detection at the level of the auditory cortex (Ceponiene et al. 2008). The P1–N1–P2 complex is strongest over frontocentral topographical regions where it is thought to represent synchronous firing in the thalamic-cortical segment of the auditory system. The effects of age on the P1–N1–P2 response have been widely studied in response to speech and nonspeech stimuli. However, reports of effects of age on CAEPs are conflicting, whereby some studies report that older adults have larger amplitudes (Tremblay et al. 2004; Campbell and Sharma 2014), some report equivalent amplitudes (Harkrider et al. 2006; Harris et al. 2008), and others report smaller amplitudes compared to younger adults (Tremblay et al. 2004; Harris et al. 2012). In general, no differences in response latency or amplitude are evident for any of the peaks (P1, N1, or P2) when simple stimuli, such as clicks, are used to elicit the response (Figs. 6.4 and 6.5). Decreased amplitudes and increased latencies appear to occur in response to more complex stimuli and for later peaks (P2). For example, Tremblay et al. (2004) reported age-related increases in P2 response latency to speech stimuli but not simple tones (Tremblay et al. 2004). Prolonged P2 latencies but not N1 latencies were observed in older adults in response to the onset of a gap in noise, and to small changes in frequency and intensity (Harris et al. 2008, 2012). Taken together, studies assessing age-related changes in the P1–N1–P2 suggest a complex pattern that is somewhat specific to stimulus characteristics and presentation paradigm.

Despite this complexity, trends have been observed across CAEP studies related to certain experimental manipulations, which may help identify neural mechanisms contributing to age-related changes in auditory processing. For example, as aging is often associated with temporal processing deficits, many of these CAEP studies

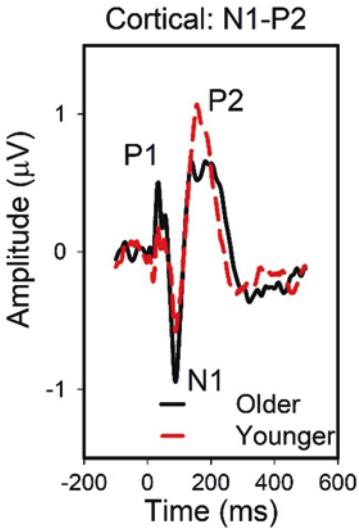

Fig. 6.4 Click-evoked P1–N1–P2 cortical responses from older adults (solid black line, $N = 38$) and younger adults (dashed red line, $N = 27$) with normal hearing. No significant differences in response latencies or amplitudes were observed across age groups

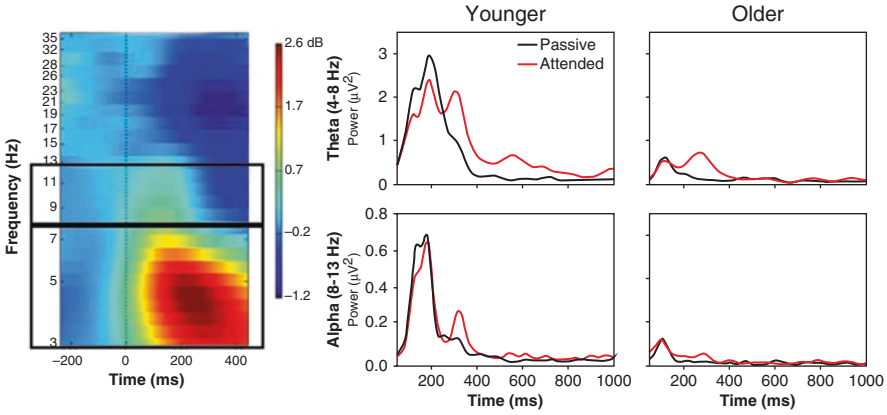

Fig. 6.5 Time-frequency analyses are performed to estimate power and phase-locking value (PLV) using a continuous Morlet wavelet transform as implemented in EEGlab, using linear spaced frequencies from 2 to 35 Hz in 2-Hz steps (left). The power spectrum is provided for a younger subject in response to a gap inserted into a broadband noise (left). Power estimates in each time-frequency bin were transformed to estimates of relative power change in dB units compared with power estimates in a baseline window. Time-frequency data were extracted for phase-locked power in the theta frequency range (top) and alpha frequency range (bottom) in younger adults (center) and older (right) adults during a gap detection task and passive and attended listening (15 ms gap duration). Theta and alpha power are largest from 100 to 400 ms, similar to the response window of the N1–P2–N2 response (left). Theta and alpha activity are larger in younger than older adults. (Data replotted from Harris and Dubno 2017)

have used experimental paradigms designed to assess the neural mechanisms that contribute to temporal processing declines. One of the most common tasks for measuring auditory temporal processing is gap detection. Together with traditional behavioral assessments of gap detection, CAEPs can begin to identify the neural mechanisms that contribute to poorer temporal processing. Behavioral assessments have suggested that poorer gap detection in older adults arises from changes in auditory processing, with limited associations with cognitive function (Humes et al. 2009). CAEP studies of the P1–N1–P2 are often performed under passive listening conditions, which are independent of attention and cognition, and therefore any changes observed in CAEPs can be attributed to age-related changes in auditory processing. Results of these studies indicate robust effects of age in response timing and amplitude and suggest that age-related deficits in auditory processing contribute to poorer temporal processing observed in behavioral measures from older adults (Lister et al. 2011; Harris et al. 2012). In Harris and Dubno (2017), EEG measures of phase locking were smaller (suggesting poorer neural synchrony) for older than younger adults and decreased as gap detection thresholds increased. Thus, CAEP findings suggest that decreased neural synchrony in the auditory system may contribute to the auditory system's reduced ability to encode rapid temporal cues.

CAEPs can be also used to elucidate the contribution of cognitive deficits to age-related changes in temporal processing. The most consistent and robust effects of age on temporal processing are revealed in behavioral performance when using complex tasks or stimuli, suggesting that in addition to the pronounced effects of auditory processing, gap detection may also depend, in part, on cognitive or attention-related factors (Pichora-Fuller et al. 2006; Harris et al. 2010). In contrast to more peripheral levels of the auditory system, attention and state of arousal can have pronounced effects on cortical EEG. While performing relatively simple tasks, such as tasks for which performance of older adults is similar to that of younger adults, older adults may be using available cognitive resources to compensate for poorer auditory processing. These compensatory effects may be observable in the CAEP, with poorer responses for older than younger adults during passive listening, but similar responses when attention is directed to the task (Alain et al. 2004).

Differences in cognitive processing and attention between younger and older adults may also be revealed in measures of temporal processing. For example, task difficulty is increased when the location of a gap in a gap detection task is varied from trial to trial, which is reflected in increased gap detection thresholds, especially for older adults (He et al. 1999). Older adults with slower global processing speed—an index of higher-level cognitive speed—are less able to compensate for increased task difficulty, which may underlie their poorer gap detection (Harris et al. 2012; Harris and Dubno 2017). Similar effects are reflected in the CAEP as differences in the response waveform during passive and attended listening (Harris et al. 2012; Tusch et al. 2016). When attention is directed to the stimuli that elicit the CAEP, the CAEP response waveform is altered, with certain peaks increasing or decreasing in amplitude and attention-related peaks emerging. This change in the response waveform from passive to attended listening, or the "attention modula-

tion" of early CAEPs, may be used to differentiate between effects of cognitive and auditory processes. These CAEP studies demonstrated possible neural mechanisms, such as neural synchrony, and characterized the differential roles of auditory- and attention-related cortical systems to age-related changes in behavior.

Similar effects of age are observed across other behavioral and CAEP studies of temporal processing. Both age and age-related hearing loss appear to alter the temporal response pattern of the auditory cortex to speech timing information, such as voice onset time (Tremblay et al. 2003). Furthermore, poorer processing of binaural temporal cues, including interaural timing and phase differences, are observed both behaviorally and in the EEG. These deficits are associated with changes in CAEPs during passive listening and are compounded by the presence of age-related hearing loss (Papesh et al. 2017; Vercammen et al. 2018).

The argument for a central effect of presbycusis, beyond that attributed to hearing loss, stems from studies such as those described earlier in this section that either find differences in cortical activity and behavior between older adults and younger adults with normal hearing or report no association between pure-tone thresholds and CAEP responses in older adults with elevated thresholds. Yet advancing age and hearing loss are difficult to disentangle. Similar to the approach of examining aging in older adults with "normal hearing" or "near-normal hearing," studies of the visual modality often report that subjects had "normal or corrected-to-normal vision." However, the contribution of visual acuity becomes more apparent and the roles of age, visual decision-making, and cognitive function become less apparent when differences in subjects' visual acuity are controlled (Porto et al. 2016). Many of the P1–N1–P2 studies discussed herein have attempted to control for differences in auditory detection by examining associations of CAEP responses with pure-tone thresholds. These studies may control for sensation level differences of the eliciting stimuli or examine group differences in CAEP responses between older adults with hearing loss and those with normal hearing. However, as discussed earlier, CAEPs of some adults with normal or near-normal thresholds may show pronounced differences from those of younger adults owing to reduced afferent input related to age-related loss or inactivity of auditory nerve fibers. Studies examining both auditory nerve potentials and CAEPs in older adults with a range of detection thresholds are needed to characterize age-related changes that occur as a result of reductions in afferent input, or those that may be independent of changes in afferent input, or those that may occur more centrally. Identifying sources of deficits throughout the auditory system, and their interactions, can improve diagnostic tools and assessments of clinical outcomes, and help guide the choice of intervention strategy. Overall, despite variability in specific findings regarding which peaks or measures are most affected, CAEPs may provide a tool for identifying the neural mechanisms that underlie age-related and individual differences in auditory processing, and for differentiating auditory and cognitive processes.

6.4.2 Associations with Neural Oscillations: Cortical Responses

The P1–N1–P2 complex reflects neural activity averaged across stimulus presentations, and therefore only activity that is time locked and phase locked to the eliciting stimulus is present in the response. However, these responses appear as minor perturbations on top of much larger intrinsic brain activity. This intrinsic brain activity appears to oscillate with periods of increased and decreased power, and its functional importance is just beginning to be understood. Induced activity of these low frequency neural oscillations in the central auditory system mediates temporal processing and speech recognition (Ahissar et al. 2001; Cogan and Poeppel 2011). Neural oscillations are typically classified in five frequency regions: delta (<4 Hz), theta (~4–8 Hz), alpha (~8–13 Hz), beta (~13–30 Hz), and gamma (>30 Hz). Examination of neuronal oscillatory activity may provide a means to characterize the combined contribution of sensory and cognitive declines, as oscillatory activity has been proposed to regulate the interaction between sensory and attention-related regions (Fries et al. 2008; Haegens et al. 2011).

Neuronal oscillations may serve to gate sensory perception at the level of sensory cortices by controlling neuronal excitability. Attention has been shown to modulate early cortical representations, enhancing the auditory signal in the theta range (4–8 Hz) and improving auditory discrimination (Kerlin et al. 2010). In addition to changes in theta activity, the degree of alpha (8–13 Hz) suppression prior to and after auditory presentation has been associated with successful task performance that may reflect selective attention (Kerlin et al. 2010; Obleser and Weisz 2012). However, research on age-related changes in neural oscillations within the auditory domain remains scarce. Studies have suggested that older adults exhibit differences in the pattern by which these networks synchronize to speech-related stimuli (Goossens et al. 2016) and the extent to which they are modulated by attention (Henry et al. 2017). Alpha in particular has been the focus of several studies because of its hypothesized role in selective attention and modulation of auditory cortex activity (Jensen and Mazaheri 2010). For example, both Rogers et al. (2018) and Tune et al. (2018) examined age-related changes in alpha power and its impact on selective attention during a dichotic listening task (Rogers et al. 2018; Tune et al. 2018). Although Tune et al. (2018) reported that associations between alpha power and task performance did not covary with age, Rogers et al. (2018) reported age-related differences in alpha modulation and associations between these modulations and task performance. Differences across studies likely stem from the variables examined and the potential impact of these age-related differences is not yet fully understood. By moving beyond simple estimates of peak amplitude or latency these EEG studies have the potential to provide a better understanding of the effects of age on neural processing and perception.

6.4.3 Environmental Enrichment: Cortical Responses

Dozens of animal models and a growing number of human studies suggest that environmental enrichment may ameliorate the detrimental effects of aging. Moreover, evidence suggests that age-related deficits in sensory systems contribute to global declines in cognitive function, and that reversing declines in sensory systems may aid cognitive functioning (Leon and Woo 2018). As noted earlier, studies of environmental enrichment and plasticity in the auditory cortex often focus on musicianship and the reintroduction of sound through amplification as the primary vehicles of enrichment. Similar to results at the level of the brainstem, musicianship improves auditory processing and older adults with musical training demonstrate enhanced CAEPs compared to age-matched nonmusicians (Zendel and Alain 2014; Bidelman and Alain 2015). Musicianship appears to not only enhance neural encoding but also strengthen the brain–behavior relationship, with older musicians exhibiting a stronger association between neural activity and speech identification than age-matched nonmusicians (Zendel and Alain 2014; Bidelman and Alain 2015). Musicianship enhances both auditory and attention-related activity (Zendel and Alain 2014) and this enhancement of attention-related activity may help explain why individuals with auditory enrichment/enhancement also demonstrate preserved cognitive function with age (Leon and Woo 2018).

Another form of enrichment is short-term auditory training. Despite growing evidence that training programs can minimize age-related sensory and cognitive decline, most of the extant literature has measured the effects of these programs behaviorally. Perceptual learning tasks, in which participants are trained to discriminate between specific auditory features (i.e., segregation of double vowels, or subtle differences in voice onset timing), show age-related differences in early CAEPs and in later attention-related components in response to the trained feature (Alain and Snyder 2008; Tremblay et al. 2014). However, changes in these early components may be the result of stimulus exposure during testing and unrelated to changes in perceptual performance (Tremblay et al. 2014). Further support for this finding comes from the auditory and cognitive training literature where researchers attempt to enhance general auditory or cognitive processes, such as processing speed or working memory, but do not manipulate a subject's responses to a specific stimulus. These training programs do not appear to alter neural activity at the level of auditory cortex (P1–N1–P2). Instead, these programs result in changes in attention-related cortex, possibly reflecting attentional resource allocation enhancement (O'Brien et al. 2013, 2017). This is somewhat surprising considering the effects of training reported at the level of the brainstem (Anderson et al. 2013b). These discrepancies could be attributed either to the fact that training and learning as assessed by these studies is driven by top-down effects of attention and not sensory processing or related to changes in brainstem and cortex interactions.

Considerable evidence is available that plastic brain changes occur as a result of hearing loss (Syka 2002), yet surprisingly few studies have examined whether the reintroduction of sound through amplification leads to differences in CAEPs in

older adults. A better understanding of amplification's effects at these higher cortical levels may inform amplification strategies and help explain the large individual differences in hearing aid success. Earlier studies measured unaided and aided CAEPs in younger adults with normal hearing (Billings et al. 2007). However, these subjects may not serve as an appropriate model for the effects of amplification in older hearing aid users as large age-related differences exist in the structure and function of the auditory system and likely the response to amplification. Studies in aided older adults have shown that the CAEP response encodes the spatial and temporal information important for speech understanding (Tremblay et al. 2006). However, the effects of amplification are still unclear and often report conflicting results. Jenkins et al. (2018) reported a decrease in latency for P1 and a decrease in N1 amplitude with amplification (Jenkins et al. 2018) while Van Dun et al. (2016) reported both increases in response amplitude with increasing gain from the hearing aid in hearing impaired adults, and confirming previous results, no effect of increasing gain in normal hearing adults (Van Dun et al. 2016). Additional studies are needed to adequately address the question of how amplification affects auditory encoding by hearing-impaired individuals. The findings that the CAEP can be elicited to phonetic features important for speech recognition in aided older adults demonstrate the usefulness of CAEPs as a tool for understanding the effects of amplification on auditory processing beyond the cochlea and auditory nerve.

6.4.4 Associations with Cognitive Decline: Cortical Responses

Hearing loss is a well-documented risk factor for cognitive impairment (Lin et al. 2011, 2013), yet the simple presence or absence of hearing loss cannot predict an adult's current or future cognitive status. This connection has led to an increase in the number of studies examining associations between CAEPs in older adults with MCI and Alzheimer's disease. Depending on the experimental parameters, differences in P1, N1, and P2 response amplitudes and latencies have been found between control groups and those with probable MCI (Golob et al. 2007; Lister et al. 2016). As discussed in Sect. 6.3.4, the pathophysiology of cognitive impairment may arise at earlier preconscious levels of processing (i.e., brainstem) and associations between brainstem and cortical potentials may improve the sensitivity and specificity of detecting cognitive impairment (Bidelman et al. 2017). These studies suggest that passively evoked measures of auditory processing, thought to occur largely independently of attention and memory, may provide a novel biomarker for differentiating healthy aging from cognitive impairment. In addition to these passively evoked auditory responses, a review of 30 articles that included auditory-evoked responses suggest that additional cortical-related potentials, such as the P300, may be able to distinguish between healthy controls and subjects with cognitive decline (Morrison et al. 2018).

6.5 Conclusions and Future Directions

In conclusion, aging is associated with a complex pattern of age-related changes occurring in the auditory periphery and throughout the central auditory system in the auditory nerve, brainstem, and cortex. Using appropriate signal paradigms and response variables, EEG provides a novel way of assessing these physiological changes. The auditory system is especially complex because each level can be affected by both aging and reductions in afferent input. These changes are not uniform across the auditory system, and the preservation of cortical responses compared to auditory nerve responses suggests some level of compensatory activity. Despite this complexity, EEG studies highlight potential neural mechanisms of disrupted temporal processing, such as reduced neural synchrony, and can identify the extent to which age-related changes in behavior are associated with auditory processing, temporal processing, and/or cognitive declines. EEG provides a potentially powerful tool for diagnosing central components of presbycusis, identifying potential targets for intervention, and for measuring changes with intervention. However, as noted throughout this chapter, several key questions remain unanswered. More definitive answers may be found through (1) longitudinal studies; (2) validation of EEG findings in animal models with known pathologies; (3) multimodal imaging studies, including the combination of MRI and EEG; and (4) a reduction in the prevalence of statistically underpowered studies. Most notable is the lack of longitudinal EEG studies characterizing age and hearing loss effects. All of the observed age-related changes in EEG reported throughout this review have been based on results from cross-sectional studies, that is, comparing averaged data across groups of healthy individuals of different ages, with the assumption that age is the only difference between these cross-generational groups, who represent widely varying health conditions, nutrition, education, employment settings, and environmental exposures. Although cross-sectional and longitudinal studies of changes in the central nervous system typically show overlap in where in the central nervous system changes occur, contradictory findings are common regarding rates of change with increasing age (Pfefferbaum and Sullivan 2015), which can only be determined for individuals using a longitudinal design.

As noted earlier, one advantage of these neuroimaging approaches is the ability to validate findings in humans in animal models with known pathology. This approach is garnering attention and will be crucial in the future development and testing of novel therapeutic interventions. In humans, several neuroimaging tools are available for studying neural function and structure, and include fMRI, near-infrared spectroscopy (NIRS), positron emission tomography (PET), and structural MR measures of gray and white matter. A multimodal approach can be used to understand the complex interplay of anatomical, functional, and physiological brain alterations that may occur with aging, and to better understand the biological significance of each imaging measure. fMRI studies routinely integrate changes in brain structure with function (Harris et al. 2009), but less is known about the structure–function relationship with EEG, particularly in the areas of auditory processing

and aging. This is surprising given that EEG studies often use structural MRI to improve source reconstruction. Although these images are used to improve spatial reconstruction, researchers have failed to conduct structural MR analyses to examine how changes in brain structure relate to the EEG. Combining functional and neuroimaging measures, particularly EEG and fMRI, can be used to validate findings in each modality and optimize both spatial and temporal resolution (Coffey et al. 2017).

Finally, consistent with the need for replication and reproducibility, additional studies of EEG should be appropriately powered. Inconsistencies in effects reported across studies may stem, in part, from the prevalence of studies that have relatively small sample sizes but perform large numbers of comparisons, thereby reducing the likelihood of replication. A better understanding of the effects of age and individual differences in the aging central auditory system will help to improve diagnostic tools, clinical outcomes, and selection of appropriate interventions that may lead to the best functional outcome, while simultaneously providing neural markers of how the system adapts to intervention and changes behavior.

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Chapter 7
Age-Related Changes in Segregation of Sound Sources

Frederick J. Gallun and Virginia Best

Abstract This chapter provides an overview of the cues listeners use to segregate sound sources and make sense of the auditory scene. These include spectral, temporal, spatial, and contextual cues. A review is also given of some of the known effects of age on sensitivity to these cues, with consideration given to the possible contributions of peripheral limitations and cognitive factors. The chapter also addresses the relevance of age-related changes in sound source segregation for the intelligibility of speech in realistic listening situations.

Keywords Aging · Auditory scene analysis · Binaural · Spectral · Stream segregation · Temporal

7.1 Introduction

One of the essential functions of the auditory system is the ability to form representations of the external world based on auditory information. This requires not only detection and identification of signals relevant to the functions of the organism, but also identification of the sources of these signals. In many cases, it is likely that multiple sources will exist in the immediate vicinity of the organism and that each will have a different meaning. Some will have important biological relevance, others will be uninteresting background noise, and some will be harmful interference.

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For example, a human on a street in even a fairly quiet town would be likely to simultaneously encounter the sounds of motor vehicles, the sounds of human voices, and the sounds of the natural world such as wind and rain, all of which could be positive, neutral, or threatening depending on the circumstances. Crucially, knowledge of the environment and the goals of the listener are essential to determining which sounds are noise and which are essential targets to be detected, identified, categorized, and remembered. To choose appropriate actions, each sound must be associated with a source, seen or unseen, in the environment.

The ability to organize and make sense of the acoustic environment, which Bregman (1990) called "auditory scene analysis," relies on a variety of different processes. A conceptual model of these processes is shown in Fig. 7.1 for an example in which speech is the sound of interest (Bronkhorst 2015). The stages of processing, shown as dark boxes with light writing, begin at the bottom of the figure with peripheral processing. This represents the transformation of the acoustical energy into a collection of amplitude patterns over time (or temporal modulations), each of which is associated with a particular spectral region. The second stage is binaural processing, in which the temporal patterns in each spectral region at each ear are compared in terms of time of arrival (interaural differences in time [ITDs]) and relative intensity (interaural differences in intensity or "level" [ILD]). While auditory scene analysis is relatively feed-forward at this early stage, note that even

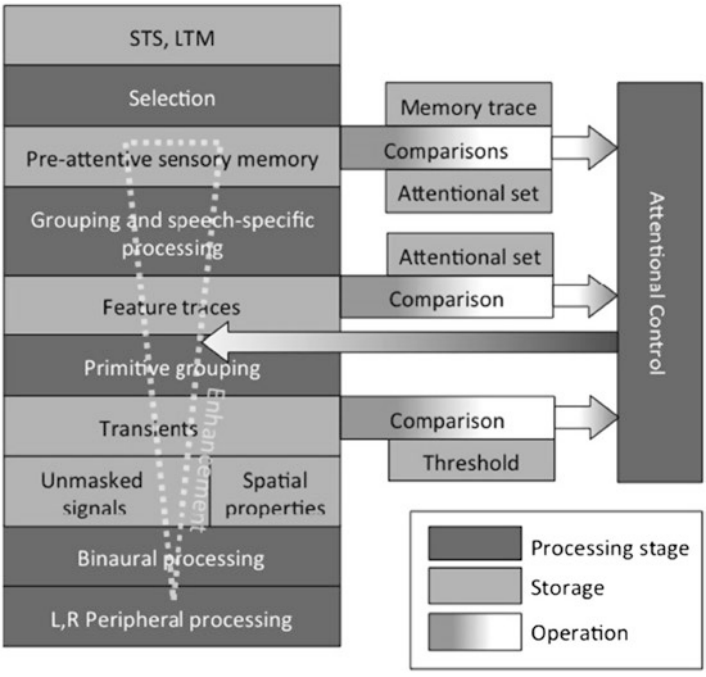

Fig. 7.1 A conceptual model of auditory scene analysis. See text for details. L, left; R, right; STS, short-term storage; LTM, long-term memory. (Reprinted with permission from Bronkhorst 2015)

here there is an automatic comparison with the current representation of the auditory scene. This way, transients or novelties in the input that might suggest alterations to the auditory scene have a chance to automatically draw attention.

In the next stage of processing, each of these spectrotemporal patterns is organized into one or more temporal sequences or streams. This process, which Bronkhorst, following Bregman (1990), refers to as "primitive grouping," has also been called "sound source segregation" or "auditory stream segregation." Shinn-Cunningham et al. (2017) and many others have argued that these streams should be considered auditory "objects" upon which attention can act (represented by the arrow between attentional control and primitive grouping). It has been argued that grouping into objects is based primarily on spectrotemporal information, after which spatial locations are assigned to individual objects (e.g., Darwin 2008). This general idea is captured in the model of Woods and Colburn (1992), whereby ITD and ILD are computed independently for each spectral region and that the combining of spatial cues occurs only once the spectrotemporal grouping process has identified the spectral regions associated with each object. It is at this point that the storage of "feature traces" is shown in Bronkhorst's model, which indicates the second type of stored information about the auditory scene that is compared with the current representation and, if a mismatch is detected, can draw attention to that spectrotemporal feature or spatial location.

The remaining operations shown in Fig. 7.1 include further grouping based on higher order factors that will be referred to as "contextual" cues. These are similar to what Bregman referred to as "schema-based" grouping cues and what have also been called "top-down" cues. These contextual cues can take many forms, but the fundamental idea is that they can influence how acoustic information is grouped as well as how selective attention is allocated to auditory objects. Contextual cues include knowledge of the stimulus (such as linguistic information for speech), knowledge of what sound sources are or are expected to be in the environment, behavioral relevance, and explicit instructions associated with a task performed in the laboratory or in the natural world. At the top of Fig. 7.1 is a box indicating the storage of information in short-term storage (STS) and long-term memory (LTM). For more details on the comparison operations by which the sensory processing stages are hypothesized to interact with storage mechanisms in order to result in the segregation of sound sources, Cowan (1998) provides an excellent discussion.

The focus of this chapter is on the effects of aging on sound source segregation. A systematic examination of the literature relevant to this topic was undertaken by the American Academy of Audiology Task Force on Central Presbycusis (AAA Task Force), as described in Humes et al. (2012). This group spent two years reviewing 165 peer-reviewed articles published between 1988 and 2009, with the goal of evaluating the evidence for the existence of what they defined as "central presbycusis." This term was taken to mean "age-related change in the auditory portions of the central nervous system negatively impacting auditory perception, speech-communication performance, or both" and is to be distinguished from *peripheral* changes and from general *cognitive* changes that may also accompany aging. This distinction is critical for the topic of this chapter, given that sound source segregation

is generally thought to rely on suprathreshold abilities (such as spectral, temporal, and spatial processing) that are neither peripheral nor cognitive but are influenced by both. Indeed, specific deficits in sound source segregation might be considered as good evidence supporting the existence of central presbycusis.

Despite the large number of studies that had reported multiple effects of aging on speech and nonspeech tasks (Anderson et al. 2018), the task force concluded that there was very little unequivocal evidence for central presbycusis as defined. On the other hand, they did conclude that there was strong likelihood of the existence of a "functional form" of central presbycusis, which they defined as the decline of "*any processing beyond the auditory periphery* that may negatively impact auditory perception and speech communication" (Humes et al. 2012, p. 663, emphasis theirs). This distinction reflects their conclusion that much of the relevant literature is so confounded in terms of the effects of peripheral hearing loss and cognitive dysfunction that it is not possible to say with any certainty that the effects reported can be anatomically localized to the auditory portions of the central nervous system.

The AAA Task Force made several broad recommendations. The first was to focus less on broadband speech measures, which were ubiquitous in the literature reviewed and were one of the main sources of peripheral hearing loss confounds owing to the failure to ensure audibility of high-frequency information in the stimuli that were presented. Instead, they recommended stimuli such as narrowband speech or nonspeech stimuli in which the amplitudes of the signals can be carefully controlled to ensure audibility. They also warned against using only low- or mid-frequency stimuli, as there may indeed be central dysfunction secondary to hearing loss or existing in the same region as the hearing loss that might be detected only with high-frequency stimuli.

The second recommendation was to focus on ensuring the reliability of the tests that were used by measuring test–retest differences and test–retest correlations, which is a charge that has been taken up by many of the agencies that fund research as well. The third recommendation was to use cognitive tests in a more uniform manner, which means using them whenever age effects are being examined and using tests that go beyond simply screening for dementia, so that the cognitive effects could be clearly differentiated from the central auditory effects.

Finally, the AAA Task Force recommended changes to the types of studies that were being conducted, with a greater emphasis on relating auditory processing abilities to the difficulties experienced by older adults in realistic listening situations. The task force recommended cross-sectional designs that include a continuum of ages (rather than just people at the ends of the spectrum) and longitudinal designs in which testing is repeated on the same participants over multiple years. In terms of the types of experiments conducted, it was urged strongly that traditional auditory processing measures using audibility-controlled stimuli be combined with electrophysiological, neuroimaging, and cognitive tests conducted by researchers expert in the relevant techniques.

The goals of this chapter are to briefly summarize the cues that underlie sound source segregation (comprehensive reviews of this topic are available elsewhere; e.g., Bregman 1990; Darwin and Carlyon 1995), to describe some effects of age on

sensitivity to these cues, and to consider the impact of these effects for the intelligibility of speech in realistic listening situations. In doing so, the chapter pays attention to the AAA Task Force report and tries to (1) acknowledge the need for the types of tests and data recommended by the AAA Task Force; (2) highlight those studies that have employed the methods recommended by the AAA Task Force and discuss the degree to which this has provided the types of evidence needed to disentangle peripheral, central auditory, and cognitive dysfunction; and (3) press forward in the belief that descriptions of the effects of the dysfunction can be informative even when the anatomical site is elusive.

7.2 Cues to Sound Source Segregation

7.2.1 Spectrotemporal Cues

A wide variety of spectrotemporal cues can be used to group sounds. When a source is excited in such a way that sound is produced, the spectral components will all start at similar times ("common onset") and if the source produces periodic vibrations there will be a common harmonicity to the components. Similarly, ongoing cues to sound source identity will follow because a physical system is generating the acoustical energy. In addition to the consistency of spatial cues over time, there will also be continuity of pitch, continuous changes in the relative levels of the various spectral components ("timbre"), and continuity of the overall level. When there is more than one set of cues, or the cues change abruptly in a manner inconsistent with a single sound source, then it is reasonable to infer that at least one additional source is present in the environment.

Bregman (1990) argues, and Bronkhorst (2015) incorporates into his conceptual model shown in Fig. 7.1, that listeners have access to an internal model of the general properties of sound sources, presumably learned over many years of experience with sound and/or acquired evolutionarily. An experience-based generative prediction ability is also included in the conceptual model of Cowan (1998) as well the computational model of saliency proposed by Kaya and Elhilali (2014) and described in Sect. 7.2.3.

A large body of work has explored the acoustic properties of sound mixtures that lead to stream segregation, or the perception of more than one source. A very common tool is the "ABA" paradigm in which two repeating tone sequences (an "A" sequence and a "B" sequence) are interleaved in time in a repeating pattern of the form "ABA ABA" with silent gaps introduced between the A tones. Listeners are played the repeating pattern and indicate (directly or indirectly) whether they perceive one or two sequences. In the most basic demonstration (e.g., van Noorden 1975), a difference in frequency, or spectral region, is introduced between the A and B tones and the repetition rates of the tone sequences are varied. When asked to try to hear the sequences as two streams or sound sources (in van Noorden's terms, trying to hear "fission" between the sequences), the frequency difference between

the tones is the most important factor. If the frequency difference is more than a few semitones, listeners report being unable to hear a single stream (or "temporal coherence") even when the repetition rate is as slow as 200 ms between tones. Figure 7.2 from Snyder and Alain (2007) illustrates the perceptual coherence associated with tone patterns that are close in frequency and the segregation of sequences far in frequency.

When asked to try to hear a single temporally coherent stream rather than trying to hear two streams, however, the time between tones interacts with the frequency difference. When the repetition time is near 50 ms, the frequency difference that supports the perception of temporal coherence is similar to that when fission is being attempted: a few semitones. When the repetition time is increased, however, the frequency separations for perceptual coherence increase as well, with repetition times of 150 ms leading to temporally coherent percepts for differences as large as an octave.

Hartmann and Johnson (1991), to overcome this effect of attentional set on temporal coherence perception, made use of the "interleaved melody" paradigm (Dowling 1973), in which two familiar melodies are played with alternating notes and the task of the listener is to identify the melodies. They varied multiple acoustical parameters of the two melodies, including frequency range, intensity, and duration. They found that differences in most of the parameters improved identification, but that the best performance was associated with conditions in which the two

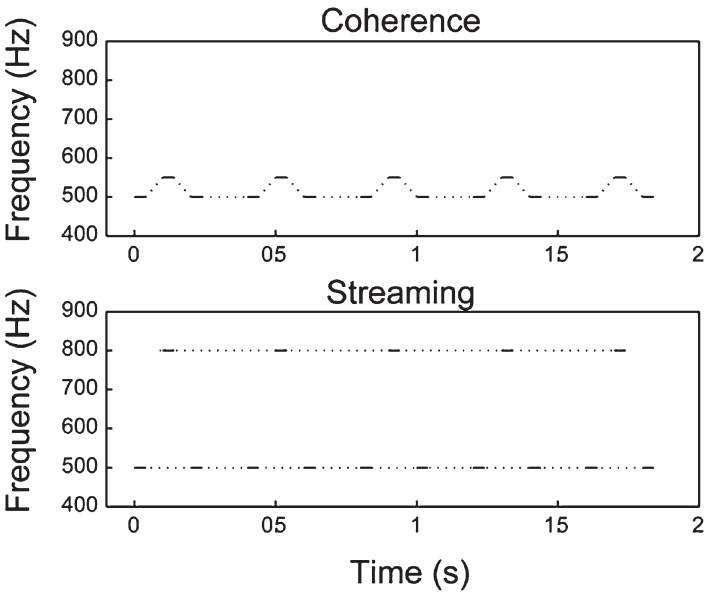

Fig. 7.2 Examples of stimuli commonly used in studies of auditory stream segregation. Solid lines indicate tones and dashed lines indicate which tones are perceived as connected to each other in the percepts of "coherence" in the top panel and "streaming" in the bottom panel. (Reprinted with permission from Snyder and Alain 2007)

melodies excited different regions of the cochlea. Rose and Moore (2000) also found support for this "peripheral channeling" explanation by increasing the intensity of the tones in the two sequences, which resulted in greater temporal coherence for the same frequency difference. They interpreted this as an effect of increased spread of excitation on the cochlea leading to reduced peripheral channel differences. Despite the superiority of peripheral channeling, differences in a variety of perceptual qualities (such as pitch and timbre) can promote segregation in the absence of peripheral channeling (see review in Moore and Gockel 2012).

The cues described in the preceding paragraphs that subserve stream segregation— such as differences in onset times and harmonicity—can also improve the audibility of a target sound that would otherwise be overwhelmed by a masker (for review see Culling and Stone 2017). For the much-studied case of extracting a speech target from noise and interference, segregation cues are thought to reveal uncorrupted "glimpses" of the target (e.g., Miller and Licklider 1950; Bernstein and Grant 2009) and much of the data are consistent with a model of the auditory system in which the perception of the listener is based on representations assembled out of these glimpses (e.g., Rhebergen and Versfeld 2005). This topic is covered more fully in Sect. 7.4.1.

7.2.2 Spatial Cues

In addition to the acoustical regularities associated with the physical processes of sound generation, the acoustics of sounds in space are also part of the generative model that listeners can access to predict what sound sources might have created the sounds they are experiencing. Inferring the spatial locations of sound sources can provide determinants of how many sounds are present and what relevance they are likely to have to the organism. The cues to sound location are created by the interaction of the head and ears with the sounds emitted by a source in the environment. Human listeners are able to detect these acoustical interference patterns both monaurally and binaurally. Binaural cues (ITDs and ILDs) are the dominant spatial cues involved in the segregation of sound sources, and as such are the main cues considered in this chapter. Nevertheless, monaural spectral cues are thought to be important for accurate localization of transient sounds in the vertical dimension and for resolving sounds coming from the front versus the back, and likely also play a role in sound source externalization (for a review of the cues to sound source location see Stecker and Gallun 2012).

There is a long history of research addressing how spatial differences can improve the detectability of a target that is obscured by a masking sound. The most straightforward example is what is called the "head shadow" effect, in which the frequency-specific ILDs associated with a target sound at one spatial location and a masker at a different location result in an improved signal-to-noise ratio at one ear relative to the case of no spatial separation (e.g., Bronkhorst and Plomp 1988). In addition, it has been well established that an ITD alone can result in substantial

improvements in the detection of either a tone (Hirsh 1948) or speech (Licklider 1948). The binaural masking level difference (BMLD) is a measure of the difference between the lowest level at which a target can be detected in the presence of a masking sound when the target and masker have identical binaural differences and the lowest level at which the target can be detected when the binaural differences are not the same for the target and masker.

The equalization and cancellation (EC) model proposed by Durlach (1960, 1963) suggests that the binaural system improves the detection of signals with binaural properties different from the masker by first equalizing the stimuli arriving at the two ears, both in level and in relative time of arrival, and then cancelling the two equalized signals. If the masker dominates the signal, then the masker will be removed by this cancellation process, leaving only the signal and improving detection. This mathematical approach continues to be one of the most successful predictors of binaural unmasking despite the fact that it does not explicitly include any information about sound source location.

Binaural cues also play a role in auditory scene analysis, although the strength of their contribution seems to depend on the particular stimulus conditions. While some have shown that differences in spatial location cannot drive the segregation of simultaneous sounds (e.g., Culling and Summerfield 1995), others have shown that ITD and ILD are useful cues to simultaneous segregation (e.g., Drennan et al. 2003; Schwartz et al. 2012). In general, however, the most parsimonious model is that monaural grouping cues are used to form auditory objects and that spatial locations are then assigned to these objects (e.g., Woods and Colburn 1992; Darwin and Hukin 1999).

The literature on "binaural interference" approaches the question from the other direction, asking whether the binaural cues imposed on one sound can be identified in the presence of a simultaneous sound with conflicting binaural cues. Overall it appears to be the case that when monaural grouping cues are present (e.g., the two sounds have common onsets and/or are harmonically related) then the individual binaural cues are difficult to access. Best et al. (2007) provided a review of this topic and presented a study that directly tested the grouping hypothesis. In that study, the interfering sound was captured into a stream of similar sounds, which reduced the tendency to group the target with the interferer, and in turn reduced the observed interference. Figure 7.3 shows the stimuli used, the amount of binaural interference produced by a single interfering tone, and the reduction in interference produced by the streaming tones.

For the case of sequential segregation, there are again mixed reports about the utility of spatial cues. Hartmann and Johnson (1991) found that differences in ITD or ILD between interleaved melodies allowed listeners to identify the individual melodies. Akeroyd et al. (2005) used the phenomenon of binaural pitch perception to introduce pitch differences into repeating noise bursts and found that listeners were able to use these cues to perceive separate streams. Other investigations have found fairly weak effects of ITD on streaming of tones (Stainsby et al. 2011; Füllgrabe and Moore 2014), whereas both monaural and binaural spatial cues can drive the segregation of broadband noises (Middlebrooks and Osnan 2012) and speech sounds (David et al. 2015, 2017).

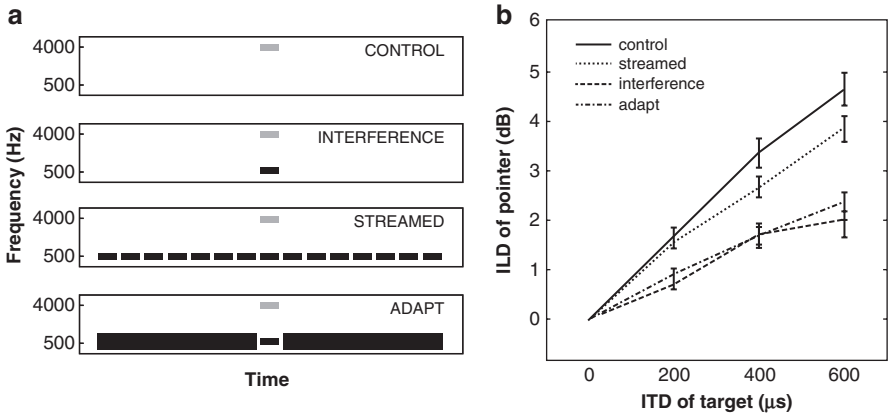

Fig. 7.3 (**A**) The stimuli used by Best et al. (2007) in a study showing how sensitivity to the interaural differences in time (ITD) of a target tone (gray dash) is influenced by a diotic interferer (black dash). When the two tones are presented together (interference condition), the perceived location of the target is drawn toward the location of the interferer. This interference is reduced when the interferer is "captured" in a stream of identical tones (Streamed) but not when the stream of tones is replaced by a band of noise (Adapt). (**B**) Lateralization responses (indicated via an interaural differences in intensity or "level" [ILD] pointer) corresponding to the stimuli in **A**, showing a reduction in the perceived laterality for the interference condition and the release from interference in the streamed condition. (Reprinted with permission from Best et al. 2007)

The well-known effects of spatial differences on performance in "cocktail party" scenarios (Cherry 1953), where multiple talkers compete both for peripheral representation and for attention, probably represent a combination of the factors discussed here (improved audibility of a target talker, and improved segregation of competing talkers). This topic is discussed in more detail in Sect. 7.4.2.

7.2.3 Contextual Cues

The third class of cues to auditory scene analysis are the contextual cues, which include prior knowledge, expectations, or intentions, and can be used to guide selective attention to particular locations (Kidd et al. 2005), time points (Jones et al. 1981), or to specific acoustical characteristics of the stimulus such as pitch (Maddox and Shinn-Cunningham 2012). Bregman (1990) suggested that context was what gave rise to the distinction between "foreground" and "background" (or target and interferer), while the primitive bottom-up grouping cues were associated merely with the formation of objects. As Bronkhorst (2015) and Shinn-Cunningham et al. (2017) point out, however, there is an interaction between bottom-up and top-down influence, which Shinn-Cunningham et al. (2017) refer to as bottom-up "salience." A computational model of bottom-up salience proposed by Kaya and Elhilali (2014) is shown schematically in Fig. 7.4, where predictive coding allows deviations from bottom-up expectancy to be detected by the model.

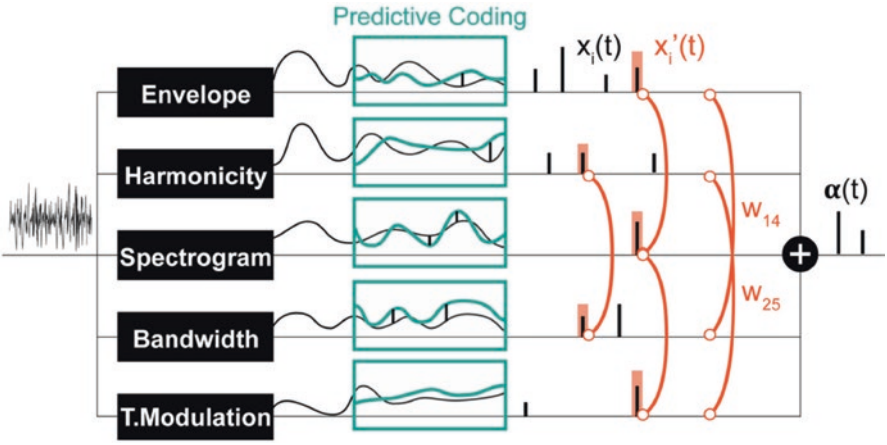

Fig. 7.4 Schematic of a computational model of saliency consisting of three stages. First, the acoustic waveform is transformed into features across five dimensions. Second, a predictive coding process tracks regularities in each dimension to detect deviations from predictions based on ongoing statistics. The output of this process is a series of times at which salient events are likely to occur, indicated as the black lines labeled $x_i(t)$. In this nomenclature, t is time and i refers to the dimension (such as envelope or harmonicity). The model recognizes the importance of multiple events occurring at the same time by adding the variable $x_i'(t)$ which boosts these co-occurring signals. In the third stage, detected deviants are integrated to create an overall saliency estimate. The final output, α(t), is a set of times at which salient events occur in the scene. (Reprinted with permission from Kaya and Elhilali 2014)

The importance of expectation in stream segregation was studied by Dowling et al. (1987), who used the interleaved melodies task of Dowling (1973) to explore the deployment of attention. The task was to make judgments of the pitch of one note of an interleaved melody, which could either occur at an expected point in frequency and/or time or at an unexpected point. Performance was better when the notes were consistent with expectations, supporting the idea that listeners were narrowing their attentional focus to particular spectrotemporal locations.

Further evidence for top-down influences on sound source segregation is the phenomenon of "build-up," in which the perception of a tone sequence tends to move from hearing one stream to hearing two streams over the course of repeated exposure. Carlyon et al. (2001) used both attentional manipulations and patients with visual neglect (who are unaware of a particular region of visual space) to demonstrate that the buildup of streaming is influenced by the voluntary allocation of attention to the sequence of tones. When the participants were required to attend to another task or, in the case of the visual neglect patients, were unable to allocate attention to the side with the sequence of tones, the proportion of the time that two streams were perceived decreased. This result interacted with the frequency difference between the streams, leading to the conclusion that there are two different factors controlling segregation, one that is automatic and driven by acoustical factors and another that is under voluntary control (Bregman 1990; Snyder and Alain 2007).

Contextual cues play a particularly important role in the segregation of acoustic mixtures containing speech. At the most basic level, it is clear that listeners use learned knowledge about speech patterns to identify speech in mixtures and to distinguish speech from nonspeech sounds. Moreover, the salience of speech can greatly influence a listener's perception and guide their attention. Salience can be based on explicit knowledge, such as when one hears their own name (Moray 1959) or it can involve implicit knowledge, such as when one hears speech spoken by a familiar talker (Souza et al. 2013) or in a familiar language (Brouwer et al. 2012). This topic will be touched on further in Sect. 7.4.3.

7.3 Age-Related Changes in Sensitivity to Segregation Cues

The following sections review the evidence for age-related changes in the various processes driving auditory scene analysis. Section 7.3.1 describes studies showing that temporal processing is affected by aging, independently of or interacting with, peripheral hearing loss. Section 7.3.2 is concerned with the question of whether or not spectral overlap of sound energy from competing sources is more problematic for older listeners as compared with younger listeners. Age effects related to spatial information are treated in Sect. 7.3.3 and to contextual information in Sect. 7.3.4.

7.3.1 Sensitivity to Temporal Cues

Several reviews are available that consider the effects of aging on various aspects of temporal processing (e.g., Fitzgibbons and Gordon-Salant 2010; Pichora-Fuller et al. 2017). Which of these aspects are most important for sound source segregation is still not well understood. One issue is that there are multiple time scales at which temporal processing is important. Furthermore, it is not clear that the same mechanisms support faster and slower temporal processing abilities.

The fastest time scale is that associated with the frequency of the components of a sound. The coding of information at this time scale is based both on which parts of the cochlea are activated by the acoustical waveform and on the degree to which the auditory nerve can fire in synchrony with the movements of the basilar membrane (Sachs and Young 1979; Young and Sachs 1979), or what is known as sensitivity to temporal fine structure (TFS; Moore et al. 2012). The rate of firing of a given auditory nerve fiber also codes information related to the harmonic structure of a sound source, owing to rapid fluctuations based on the interactions of components that all fall in the receptive field of the nerve fiber (Winter 2005). Defined in this way, it is clear that TFS provides access to multiple types of information about both speech and environmental sounds (such as pitch and binaural information) that can be used to identify them and distinguish them from other sounds. Reduced sensitivity to TFS is thus very likely to have consequences for the segregation of competing sounds.

Ross et al. (2007) provided human physiological data showing age-related declines in interaural phase sensitivity that have been interpreted as evidence that the highest frequency at which the auditory nerve can be "phase-locked" to the input waveform is dependent upon age. Grose and Mamo (2010) provided corroboration of these results and extended them to include both monaural and binaural cues (Grose and Mamo 2012). Figure 7.5 shows data from Grose and Mamo (2012) in which listeners with normal hearing are shown to vary in sensitivity to frequency modulation based on age.

In accordance with the recommendations of the AAA Task Force (Humes et al. 2012), Füllgrabe (2013) provided data from a large (N = 102) cross-sectional sample of listeners across the age range also suggesting that both monaural and binaural TFS sensitivity decline with age. One difficulty with interpreting the data on TFS sensitivity among older listeners is that there are almost always slight differences between the audiometric thresholds of the younger and older listeners. Bernstein and Trahiotis (2016, 2018) used a set of binaural tasks to show that it was possible to see differences in binaural sensitivity among people with audiometric thresholds differing by 15 dB or less, even when all thresholds were in the normal range. Furthermore, animal models of aging show that even when audiometric thresholds are unaffected, auditory nerve fibers can be damaged or missing in older animals (Liberman 2017).

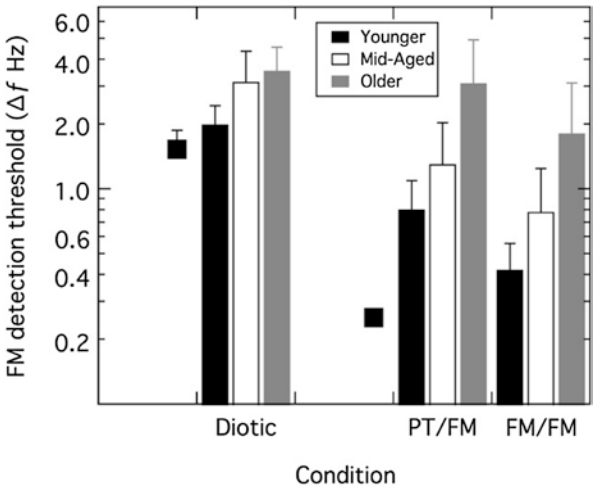

Fig. 7.5 Listeners with normal hearing vary in sensitivity to frequency modulation based on age. Black bars show thresholds for younger listeners for tones presented diotically or with a pure tone (PT) in one ear and frequency modulation (FM) in the other. The black square replots data from younger listeners tested by Witton et al. (2000) in the same conditions. An FM/FM condition, where the frequency rises in one ear and falls in the other is also plotted. White bars show data for middle-aged listeners and gray bars data for older listeners, all with hearing thresholds in the normal range. (Reprinted with permission from Grose and Mamo 2012)

At slower time scales, there is evidence that aging affects sensitivity to temporal envelopes, which is consistent with the impacts of aging on the central auditory system beyond the auditory nerve. Neurophysiological data from younger and older monkeys (described in detail in Chap. 5 by Recanzone) revealed that temporal coding was significantly better for the younger as compared to the older monkeys. In humans, studies have examined the ability of listeners to track slow envelope fluctuations associated with modulation of the sound source energy over time, such as that accompanying the opening and closing of the mouth during speech. The evidence for aging effects on sensitivity to amplitude modulation at these low rates is less prevalent than that for higher rates, suggesting that perhaps temporal modulation sensitivity at low rates is largely preserved (e.g., Takahashi and Bacon 1992; Grose et al. 2009).

One of the most well studied effects of aging is that associated with the detection of silent gaps (usually in the range of 2–10 ms) between pairs of brief stimuli or introduced into longer ongoing stimuli. Schneider et al. (1994) found that older listeners require longer gaps between brief markers than do younger listeners, even after accounting for differences in audiometric thresholds. Gordon-Salant et al. (2006) used speech cues and reached a similar conclusion, demonstrating that older listeners with normal hearing need longer durations of speech cues in order to make distinctions between words such as "dish" and "ditch" or "wheat" and "weed." These studies, like many others that have examined aging and temporal processing, found effects both of hearing loss and of aging, but were able to control for the hearing loss effects in order to show independent effects of age.

One large cross-sectional study (Ozmeral et al. 2016) investigated more than 1000 participants ranging in age from 18 to 98, allowing the authors to both select a subsample with normal hearing ($N = 434$) and to perform a statistical analysis in which hearing thresholds were removed from the equation. These data, unlike those from studies in which a younger group is compared with an older group, or where the age range is sampled unevenly, were able to show that gap detection thresholds worsen at a rate of 1.05 ms/decade until the sixth decade of life, at which the rate accelerates to 1.23 ms/decade. This work, due to the cross-sectional sampling and the very large sample size, is consistent with the recommendations of Humes et al. (2012).

There have also been many studies that have examined age effects on temporal sensitivity using gap duration *discrimination*, which have shown impairments at relatively longer time scales (tens to hundreds of milliseconds). For example, when the silent interval between two markers is varied, the increase in the silent gap needed to detect a change is longer for older adults (Fitzgibbons et al. 2007), and even larger age differences are observed when the tonal markers on either side of the gap differ in frequency (Lister et al. 2002). In fact, Grose et al. (2006) found evidence of age effects on the different-frequency gap discrimination task with a group of middle-aged participants. Using another task involving temporal judgments across relatively longer time scales, Fitzgibbons et al. (2006) found that the ability to report the order in which a series of tones was presented declined with age, with the greatest effects occurring at the highest presentation rates.

It is unclear what mechanisms are responsible for age-related declines in gap detection and discrimination, and as Humes et al. (2012) point out, mechanisms can be difficult to determine from behavioral measures alone. Lister et al. (2011) provided electrophysiological evidence regarding the differences between younger and older listeners when presented with silent gaps of various durations. In response to these stimuli, it is possible to record electrical signals at the scalp that reflect neural activity. In the case of the signals recorded by Lister et al. (2011), it is presumed that the early responses (50–100 ms) reflect primary auditory cortical processing and that later responses (200–300 ms) reflect frontal areas associated with attention, memory, and decision making. For further discussion of the sources of these signals see Harris (Chap. 6). Summary recordings from Lister et al. are shown in Fig. 7.6. Consistent with the behavioral differences between groups, the evoked responses had significantly different time-courses and amplitudes in the older listeners. One of the most striking results was the greater response to differences in the frequencies of the markers as compared with the gap itself in the older listeners, suggesting that the frequency change was more salient than the gap. Another important finding was

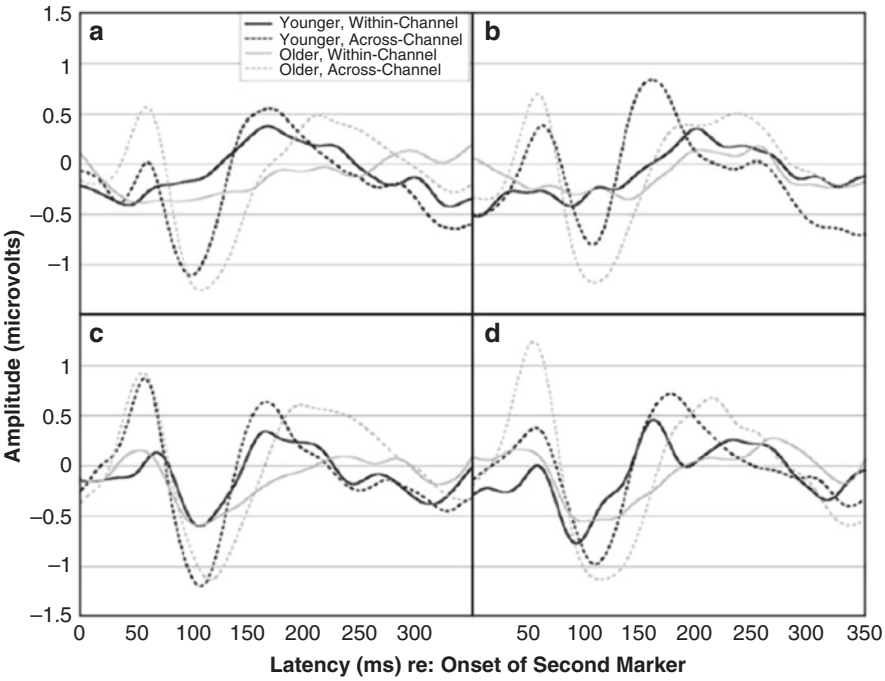

Fig. 7.6 Electrophysiological evoked responses to gaps in noise stimuli for younger (black lines) and older (gray lines) listeners. Whether the noise stimulus was in the same frequency region before and after the gap ("within-channel," solid lines), or different before and after ("across-channel") and regardless of whether the gaps were clearly detectable (**A** and **D**), near threshold (**C**), or below detection threshold (**B**), later and reduced amplitude gap responses (peaks around 150 ms) were observed in the older group. (Reprinted with permission from Lister et al. 2011)

that the topography showed a greater influence of frontal areas for older listeners, which suggests that the older listeners may have been forced to use cognitive strategies to detect the gap rather than relying on automatic detection processes at the level of auditory cortex.

Future work in this area will need to continue to leverage electrophysiological measures and include neural imaging to understand of the basis of temporal processing difficulties in older listeners. In addition, it may be important to measure the ability of older participants to perform the attention and memory tasks inherent in making temporal judgments. The role of cognition is considered in more detail in Sect. 7.3.5 as it relates to the use of contextual cues.

7.3.2 Sensitivity to Spectral Cues

Age-related changes in spectral processing may also have consequences for sound source segregation. Fitzgibbons and Gordon-Salant (2010) and Pichora-Fuller et al. (2017) reviewed the literature on frequency discrimination and other spectral processing abilities in older listeners. Many studies report effects of aging on frequency-modulation detection thresholds, which can be attributed to poor TFS sensitivity as discussed in Sect. 7.3.1 (see Fig. 7.5; also He et al. 2007; Whiteford et al. 2017). Another measure of sensitivity to spectral information is the width of the putative auditory filter. Peters and Moore (1992) examined auditory filters using the notched-noise method of Glasberg and Moore (1990) and found that while hearing-impaired listeners tended to have wider filters than did those with normal hearing, there was no reliable tendency for older listeners with hearing impairment to have wider filters than younger listeners with hearing impairment. On the other hand, when forward masking rather than simultaneous masking was employed, the results have been mixed, with some studies pointing to an effect of aging (Sommers and Gehr 1998; Dubno and Ahlstrom 2001) and others suggesting that older listeners do not show any broader tuning with forward masking (Gifford and Bacon 2005). In their review, Fitzgibbons and Gordon-Salant (2010) point out that it is possible that some of the differences in results could be the result of small differences in cochlear function between the younger and older groups.

In an effort to examine the combined effects of temporal and spectral resolution in listeners with hearing loss, Mehraei et al. (2014) measured sensitivity to spectro-temporal modulation. The smallest modulation depth at which listeners can detect spectrotemporal modulation has been shown to be predictive of speech intelligibility in noise among listeners with hearing impairment (Bernstein et al. 2013) even once the differences in hearing thresholds among the participants have been taken into account. Mehraei et al. (2014) found that while there were robust effects of hearing impairment, which again correlated with speech intelligibility, there were no reliable effects of aging independent of hearing status. To date, however, no studies have investigated sensitivity to spectrotemporal modulation for listeners across the age span without impaired hearing.

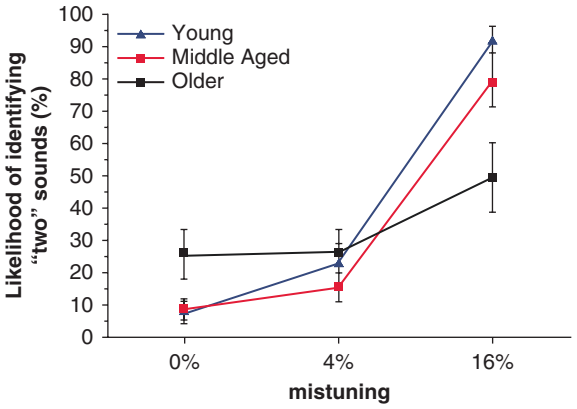

Fig. 7.7 Likelihood of reporting two sounds given various amounts of mistuning of a harmonic for younger, middle-aged, and older listeners. (Reprinted with permission from Alain and McDonald 2007)

Sensitivity to harmonicity, and the ability to detect inharmonicity, is fundamental to the segregation of concurrent sound sources. Older listeners are less sensitive than younger listeners to the mistuning of a harmonic, needing a larger mistuning for the perception of two sources (Alain and McDonald 2007; see Fig. 7.7). Moreover, in a simplified double vowel paradigm, older listeners are less accurate at identifying the vowels than younger listeners and have longer response times (Snyder and Alain 2005).

Consistent with the recommendations of the AAA Task Force, a number of studies have used electrophysiological measures to examine the ability of the aging auditory system to perform sound source segregation based on spectral cues. Although the results are somewhat mixed, in general findings suggest that age-related deficits can be observed in simultaneous segregation processes (e.g., Snyder and Alain 2005; Getzmann and Näätänen 2015) or in sequential segregation that is dependent on bottom-up processing, as probed with the mismatch negativity (MMN; Dinces and Sussman 2017). On the other hand, processes of stream segregation involving top-down strategies appear to be preserved in older listeners (Snyder and Alain 2007).

7.3.3 Sensitivity to Spatial Cues

Eddins et al. (2018) provided a review of the literature demonstrating age-related declines in the neural representation of space. At the time of that review, the strongest evidence available was associated with the hypothesis that the aging process impairs the encoding of TFS which is required for good ITD sensitivity (Sect. 7.3.1). Chapter 4 describes the mechanisms that are currently believed to be responsible for this impairment and Chap. 5 describes how these changes at the early coding stages result in increases in the spatial receptive fields at the level of the cortex.

Colburn (1982) and Moore (2014) both conducted reviews of the behavioral literature and concluded that older listeners do have poorer sensitivity to ITDs, at least for pure-tone and narrowband stimuli. Several studies have gone to great lengths to untangle the effects of age and hearing loss on ITD sensitivity by using groups varying in one or both dimensions and in general have found contributions from both (e.g., Vercammen et al. 2018). Sensitivity to ILD, on the other hand, appears to be age independent (Babkoff et al. 2002) as long as hearing thresholds are within normal limits and sounds are presented at sufficiently audible levels. For absolute localization, which relies on both ITD and ILD, the very few studies that exist suggest that older listeners are less accurate than younger listeners (e.g., Dobreva et al. 2011).

As discussed in Sect. 7.2.2 the binaural system plays an important role in helping listeners separate a sound source of interest from interfering sounds. The majority of studies that have measured BMLDs have found age-related deficits. In two examples (Anderson et al. 2018; Eddins et al. 2018), BMLDs were elevated in older as compared to younger listeners, with concomitant changes in cortical and brainstem electrophysiological measures.

Age effects have also been reported in studies that specifically examined location-based stream segregation. For example, Füllgrabe and Moore (2014) showed a reduced potency of ITDs for inducing obligatory stream segregation of sequential tones in older listeners, although they were unable to rule out that the effect was related to hearing loss.

7.3.4 Sensitivity to Contextual Cues

Contextual cues as defined in Sect. 7.2.4 can take many forms, and thus there are many ways in which aging could reduce sensitivity to these cues. However, older listeners may rely upon explicit cognitive processing strategies to overcome perceptual deficits to some extent. The existence of compensatory mechanisms is likely responsible for the complex pattern of results that has been reported across studies, where in some paradigms older listeners can perform as well as younger listeners, and in other paradigms the cognitive strategies cannot make up for the perceptual declines.

The most essential elements of top-down or schema-based segregation are memory and attention, which together allow the listener to form representations of what they have heard, make predictions about the sounds that are likely to come next, and deploy processing resources to the appropriate spectrotemporal and spatial locations in order to obtain evidence confirming or disconfirming these predictions. As mentioned in Sect. 7.3.2, memory is involved in even the most basic psychoacoustical tasks, which may explain why there is conflicting evidence regarding age effects for several basic auditory sensitivities (e.g., the use of slow rate temporal information; Takahashi and Bacon 1992; Fitzgibbons and Gordon-Salant 2010). Some of the strongest evidence for impaired sensory memory in older listeners comes from

a meta-analysis of the MMN in response to a change in the acoustical characteristics of a stream of sounds (Cheng et al. 2013). The analysis included data from nine studies comprising 182 young adults and 165 older adults. Significant differences between groups were found when the deviant stimulus was different in duration, frequency, or timing relative to the other stimuli. This was true both for stimuli with short gaps between stimuli (<2 s) or long gaps (>2 s).

Behavioral evidence is also consistent with the hypothesis that aging results in impairments in sensory memory. For example, Gallun et al. (2012) presented younger and older listeners with short sequences of four noise bursts varying in frequency and intensity. The task of the listener was to compare the intensity of a target burst in the middle of the sequence with the intensity of a comparison burst presented before or after the sequence. The intensities could be the same or different and the level was varied adaptively to find the smallest difference detectable by each listener. There were no age differences in the ability to detect differences in intensity when the comparison stimulus was presented before the sequence, but when the comparison burst was presented after the sequence, older listeners performed significantly more poorly than did younger listeners on the task.

7.4 Age-Related Changes in the Segregation of Speech from Competing Sounds

7.4.1 Segregation Based on Monaural Cues

The spectral and temporal cues described in Sect. 7.2.1 are also important for understanding speech in multiple-source settings. In particular, when a listener is trying to extract the speech of one talker from noise, or from competing talkers, segregation cues serve to identify frequencies and time points that contain reliable information about the target talker. The process of understanding speech in competition then appears to involve assembling these glimpses into a set of spectrotemporal patterns that can be interpreted as speech. Early evidence for this came from Miller and Licklider (1950), who found that when ongoing speech is interrupted at a rate of 15 times/s, it is nearly as intelligible as when it is uninterrupted, even though the interruptions removed 50% of the speech waveform. Cooke (2006) proposed that incomplete pieces of the spectrotemporal information in a speech target are tracked over time and integrated to form a prediction of what the speaker is saying. A computational model was developed that used as input a smoothed and compressed representation of the envelope of the modeled basilar membrane output in response to the input speech and noise waveform. The model was able to predict human performance very accurately by assembling glimpses over time and filling in the missing information.

The results described in Sects. 7.3.1 and 7.3.2 suggest that older listeners should have more trouble detecting glimpses of target speech in a mixture due to their reduced temporal sensitivity and spectral resolution. The vast literature on speech

perception in older listeners is consistent with this idea, demonstrating poorer speech intelligibility relative to young listeners for both noise maskers and speech maskers (e.g., Helfer and Freyman 2008, 2014). Moreover, Bologna et al. (2018) confirmed that the poor performance of older listeners in speech mixtures does stem in part from a degraded ability to piece together speech glimpses. Looking at the problem from a slightly different point of view, experiments examining the time course of intelligibility suggest that older listeners are *slower* than younger listeners at extracting a target talker from competing talkers (Ben-David et al. 2012; Ezzatian et al. 2015).

Age effects have generally been reported in experiments that have specifically probed the benefits of various segregation cues for speech intelligibility. For example, Lee and Humes (2012) looked at the benefit of fundamental frequency and sentence-onset differences using a competing-talker task and found that older listeners (especially those with hearing loss) obtained the least benefit from the cues. On the other hand, Helfer et al. (2016) reported that older listeners were particularly impaired in their ability to understand speech when the competing speech was time-aligned with the target speech but performed much more similarly to younger listeners when the competing talkers were presented with a temporal asynchrony in the word onsets and offsets. This suggests that older listeners were able to make effective use of temporal envelopes for segregation under those conditions. Besser et al. (2015) found that older listeners gained less benefit than young listeners from differences in voice for a speech-on-speech test. However, even though their older listeners had "good" audiograms, the results indicated that the use of the voice cues was related to high-frequency audiometric thresholds, highlighting again the difficulty in attributing these difficulties to age (or central presbycusis).

7.4.2 Segregation Based on Binaural Cues

It is well known that speech intelligibility is improved when sources of interference (be they noise or other talkers) are spatially separated from the target message in the horizontal plane. When the interferer is noise, this improvement comes about both from head-shadow effects and from binaural unmasking based on ITDs (see Sect. 7.2.2). There is a wealth of studies demonstrating that older listeners show a reduced benefit of spatial separation for speech-in-noise perception (e.g., Duquesnoy 1983). Some of this can be attributable to the loss of head-shadow benefits due to high-frequency hearing loss, but even when carefully accounting for this, it appears that older listeners are less able to use the available interaural difference cues to obtain a benefit (e.g., Dubno et al. 2008).

When the interferer is another talker, or a sound with speech-like fluctuations, such that segregation based on monaural cues is challenging, spatial differences provide a rather robust segregation cue. In this case it is believed that *any* spatial cue that leads to a perceived separation of the competing sounds can also enhance segregation and ultimately intelligibility. Again, there are numerous studies demonstrating a reduced spatial benefit under these conditions for older listeners

(e.g., Helfer and Freyman 2008; Besser et al. 2015). However, many studies have been unable to dissociate age and hearing loss, and fewer still have been able to identify distinct mechanisms that might be responsible for the negative effects of age and/or hearing loss. One of the few exceptions is King et al. (2017), who showed that older listeners with better low-frequency hearing were more able to take advantage of TFS cues to achieve better spatial release from masking.

The literature on the effects of age and hearing loss on spatial release is a good example of where the issues raised by the AAA Task Force (Humes et al. 2012) have been responsible for conflicting results even from studies involving large numbers of participants. Marrone et al. (2008) found no statistically significant age effect but used a relatively small sample of listeners with rather severe hearing losses, and thus likely lacked the statistical power to reveal a contribution of age in addition to hearing loss. Similarly, while Glyde et al. (2013) used a large sample of 80 participants in the age range from 7 to 89 years of age, all of the listeners under age 18 and over 75 had hearing in the abnormal range, while only two of the listeners between ages 18 and 40 had abnormal hearing. Perhaps not surprisingly, the statistical model did not reveal a significant effect of age independent of hearing loss. Gallun et al. (2013) attempted to address this issue by recruiting 52 listeners varying in age from 18 to 76 who all had hearing that was in the range of normal to moderately impaired. In this case, independent contributions of age and hearing loss were observed.

Using similar paradigms, Srinivasan et al. (2016) and Ellinger et al. (2017) both demonstrated an aging effect independent of the effect of hearing loss. However, other studies that have attempted to control for hearing loss by using audiometrically matched groups (e.g., Füllgrabe et al. 2015) or older listeners with normal hearing (e.g., Besser et al. 2015) found no appreciable effect of age per se on spatial release from masking. Methodological differences might partially explain these discrepancies. The studies that have not shown age effects tended to use very large spatial separations between target and maskers, whereas Srinivasan et al. (2016) found that age effects are stronger for smaller separations. One potential explanation for this is that performance at small separations may depend more critically on ITD cues (which are particularly susceptible to aging; see Sect. 7.3.3), whereas performance at larger separations may benefit from head-shadow effects that are less sensitive to aging. Interestingly, when spatial separation is achieved only *perceptually* (with no possible acoustic benefit) then older and younger listeners appear to benefit equally (Li et al. 2004).

One of the recommendations of the AAA Task Force (Humes et al. 2012) was that more use should be made of electrophysiological paradigms. Papesh et al. (2017), in one of the few studies that has explored spatial sensitivity using electrophysiology, found that while age and hearing thresholds were strong predictors of speech understanding with spatially separated maskers as well as spatial release from masking, the strongest predictor was the electrophysiological response to a change in binaural cues. Indeed, once this cue was added to the statistical model, neither age nor hearing impairment was a significant predictor of spatial release from masking, although age was still a significant predictor of speech understanding with spatially separated maskers. Studies such as this one may help lead the way to

a mechanistic interpretation of the effects of aging, which has the possibility of helping to untangle much of the confusion currently in the literature.

7.4.3 Segregation Based on Contextual Cues

Many studies have shown that older adults are adept at making use of various forms of context when segregating speech from background speech. For example, contextual cues indicating *who* to listen to can be beneficial. Souza et al. (2013) and Johnsrude et al. (2013) both reported that older listeners can benefit from a familiar target talker (someone they had known for more than 15 years) when speech is masked by noise or a competing talker. Ezzatian et al. (2011) reported that older listeners benefited from an auditory "primer" designed to help the segregation of a target talker from a mixture. However, Freyman et al. (2017) examined the benefit of a written primer, which helps speech to pop out from a background of babble and found that this automatic priming process is weaker in older than in younger adults. When competing sounds are distributed in space, older listeners make good use of prior knowledge about *where* to listen (e.g., Getzmann et al. 2014; Getzmann and Washcer 2017). When such cues are not available and attention must be switched instantaneously between locations, older listeners experience particular difficulties (e.g., Singh et al. 2013; Getzmann et al. 2015).

7.5 Realistic Listening Environments

Given the fundamental importance of sound source segregation for the ability of humans to function in real-world situations, it seems intuitive that many of the effects of age reviewed in Sects. 7.3 and 7.4 would have an impact on the everyday listening experience of older people. Certainly, in subjective reports, older (and even middle-aged) listeners indicate that they find real-world listening situations demanding. For example, Banh et al. (2012) assessed the real-world experiences of 48 young and 48 older listeners with audiometrically normal hearing by administering the Speech, Spatial and Qualities of Hearing Questionnaire (the SSQ). Scores on the SSQ were consistently lower in the older group, suggesting that they experience more difficulties with many of the items assessed. As pointed out by Helfer et al. (2017), self-report data often reveal individual differences that are not well captured by laboratory studies. On the other hand, questionnaires and other self-report tools are generally too broad to pin down the source of the difficulties experienced. For example, it would be difficult to say with certainty which items assessed in the SSQ depend on the ability to segregate sounds.

Much of the data reviewed in the previous sections came from laboratory experiments involving relatively artificial stimuli and environments. In most, the stimuli were simple tones or noises, while even the speech stimuli were often highly

artificial, involving limited vocabularies, carefully time-aligned competition, and sentences that were unconnected to each other across trials. These artificial conditions are essential for careful control of the multiple factors that could potentially interact in creating deficits associated with aging and are consistent with the recommendations of the AAA Task Force. On the other hand, the long-term goal of this research is to help understand the difficulties experienced by older listeners outside of the laboratory. There is now increasing effort being put into bridging the divide between laboratory and realistic listening environments for better understanding the consequences of hearing loss and hearing aids (e.g., Wolters et al. 2016; Wu et al. 2018; Beechey et al. 2019). This line of research has a lot of potential for bringing new insights into age-specific effects on real-world listening experiences.

In a series of studies from the National Acoustic Laboratories, the effects of adding realism both to the listening environment (Best et al. 2015) and to the listening task (Weller et al. 2016; Best et al. 2018) were explored in young and older listeners. In these studies, older listeners tended to show an even larger deficit as the complexity of the scenario was increased, although it was generally not possible to rule out effects of hearing loss, which was confounded with age in the relatively small subject samples used. Even in more typical laboratory test paradigms, it has been noted that age effects tend to be more prominent as the complexity of the stimuli or task increases (e.g., see review by Helfer et al. 2017). Certainly, the amount of complexity or "realism" present in the various tasks and stimuli discussed in previous sections of this chapter may also have affected the results and may be partially responsible for some of the apparent discrepancies in the conclusions.

For example, in Sect. 7.4.2 the findings of Glyde et al. (2013) were contrasted with those of Gallun et al. (2013). While the former study found no significant effect of age on spatial benefits for speech segregation, the latter did, and it was suggested that the discrepancy reflected the makeup of the subject pool and ultimately the statistical power available for observing age effects. However, another difference between the two studies was the structure of the speech materials used. While Gallun et al. used target and masker sentences with limited semantic content that were very similar in syntactic structure and vocabulary, Glyde et al. embedded their target sentences in ongoing coherent stories, which is arguably a more "realistic" situation and certainly one that allows for a greater use of context and semantic knowledge to distinguish the target from the masker. Potentially, differences of this nature could be responsible for the discrepant findings between these two studies and across other studies in the literature.

7.6 Conclusions and Future Directions

Despite a wide variety of results and some clear inconsistencies, there appears to be ample evidence in the literature for age-related changes in sensitivity to the cues needed for sound source segregation. While these are generally negative changes, there are examples in which the performance of older listeners is as good as that of

younger listeners, possibly due to compensatory mechanisms. Overall, however, the changes in sensitivity discussed appear to influence speech understanding both in the laboratory and in real-world listening situations.

More research is needed to confidently address the question of whether age-related changes in sound-source segregation fall into the definition of central presbycusis, meaning that they do not arise directly from peripheral loss and are not symptomatic of a more general cognitive decline. Furthermore, it is not even clear exactly how to distinguish auditory-system specific deficits from general neural declines that might affect multiple sensory and cognitive processing abilities. For progress to be made in this area it will be essential to follow the recommendations put forward by the AAA Task Force. In particular, a stronger focus on stimulus control is needed to account fully for peripheral loss, and the consistent use of cognitive measures would be useful for understanding the contribution of non-auditory factors.

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Chapter 8
Causes and Consequences of Age-Related Hearing Loss

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Abstract Hearing loss in older adults is a national and global health priority. Fifty percent of adults over the age of 60 years are impacted by a clinically meaningful hearing loss, with that number increasing to every two out of three adults over the age of 70. There is also growing recognition that hearing loss is associated with increased risk for health conditions including dementia and falls. This chapter describes what is known about age-related hearing loss from population-based epidemiologic studies, including the prevalence (burden of existing hearing loss) and incidence (new cases of hearing loss), and describes patterns of severity and trends

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by demographics and over time. Risk factors for hearing loss are discussed, including those for acquired (and therefore potentially preventable) hearing loss, such as noise exposure, environmental exposures, medications, and cardiovascular-related factors. Also included is epidemiologic evidence for possible consequences of age-related hearing loss, beginning with a framework for understanding how epidemiologic and clinical research is synthesized and evaluated to determine the relationship between an exposure and an outcome. Evidence is then presented for the association between age-related hearing loss and communication and functional geriatric outcomes, including dementia, cognitive impairment and decline, depression, physical function and disability, social engagement, and healthcare utilization. A theoretical biological mechanistic rationale is also provided as to why age-related hearing loss may possibly be related to these important functional outcomes in older adults.

Keywords Association studies · Causal inference · Cognitive decline · Confounding factors · Dementia · Depression · Epidemiology · Epidemiologic methods · Falls · Physical function · Population-based studies · Prevention · Risk factors · Social engagement

8.1 Introduction

Age-related hearing health in older age has emerged as a national priority in the United States (President's Council of Advisors on Science and Technology 2015; National Academies of Science, Engineering, and Medicine 2016) and globally (Chadha et al. 2018). This recognition is due in part to the large number of adults with hearing loss—more than 50% of US adults aged 60 years and older have a clinically meaningful hearing loss (Lin et al. 2011a)—and in part to recent investigations suggesting that hearing loss is associated with important health conditions, including dementia (Livingston et al. 2017), mental health (Blazer 2018), physical disability (Chen et al. 2015), and falls (Jiam et al. 2016).

Hearing loss negatively impacts everyday communication and quality of life for older adults. Although hearing loss is treatable, the majority of older adults with hearing loss do not use hearing aids (Chien and Lin 2012; Dawes et al. 2014; Humes et al., Chap. 11). That so many who could potentially benefit go without treatment is likely due to issues related to accessibility and affordability (NAS 2016), as well as to the common misconception that hearing loss is just a normal part of getting older. While it is true that some well-established risk factors for hearing loss cannot be changed, including increasing age, race/ethnicity, and sex, there are modifiable factors that increase risk for hearing loss, including noise exposure and perhaps even cardiovascular and lifestyle factors. As such, age-related hearing loss may not

be an inevitable consequence of aging but a condition that may possibly be delayed or prevented.

This chapter summarizes epidemiologic data about the burden of age-related hearing loss and reviews the current state of the science from population-based studies for its causes, including those that are potentially modifiable, and its possible downstream sequelae. Understanding these relationships is necessary to inform public health efforts to potentially prevent hearing loss and its consequences in older adults.

8.2 Who Has Age-Related Hearing Loss?

Hearing may be assessed using multiple instruments in clinical or research settings, ranging from basic physiologic measures, such as otoacoustic emissions, to patient self-report of hearing-related communicative function. Although each measure captures different facets of hearing health, as the goal of this chapter is to identify risk factors for, and consequences of, peripheral hearing loss, the primary measure discussed is pure tone audiometry. Speech-in-noise tests may also be collected in large-scale, epidemiologic studies. Although they can reveal functional hearing difficulties in the absence of clinical loss, because they involve central cortical processing in addition to peripheral transduction of sound, they are not discussed in this chapter.

8.2.1 Measurement of Age-Related Hearing Loss

In epidemiologic studies, hearing loss may be measured by investigators or self-reported by participants. Pure-tone air-conduction audiometry is considered the gold standard to measure the peripheral ability of the cochlea to encode a simple pure tone. Traditionally measured in a sound-proof booth, application-based systems with noise monitors offer a portable alternative for measuring pure tone thresholds. Questionnaires are less costly and less time-consuming to collect in large epidemiologic studies. However, classification of hearing impairment by self-report is imperfect compared to audiometry. Many individuals with hearing impairment measured by pure tone audiometry self-report no hearing difficulty (Agrawal et al. 2008; Choi et al. 2016; Humes et al., Chap.11), but some who have audiometric thresholds within normal limits will self-report hearing difficulty (Tremblay et al. 2015).

In a nationally representative study of community-dwelling adults in the United States aged 50 years and older, demographic factors were associated with accuracy of self-reported hearing loss, as well as the direction of the misclassification. Older age, particularly age 70 years or older, and a less than a high school education were both associated with a systematic underreport of hearing loss. By contrast, younger

participants and participants with a college degree were more likely to over report hearing loss (Kamil et al. 2015). Importantly, these factors are often associated with disease risk, and so choice of measurement method for hearing loss may therefore result in different estimates of hearing-outcome associations (Choi et al. 2016). Self-report, as a measure of the *perceived* impact of hearing loss, likely captures a different dimension of hearing loss than objectively measured hearing loss. Both objectively measured and perceived hearing loss may be important for health, but researchers should not assume that hearing loss by self-report is representative of objectively measured hearing loss (Choi et al. 2016).

8.2.2 Prevalence (Existing Cases) of Age-Related Hearing Loss

Hearing loss affects nearly two-thirds of adults aged 70 years or older (Lin et al. 2011b; Jun et al. 2015), making it one of the most prevalent chronic conditions in older adults. Prevalence estimates from population-based studies depend strongly on the definition of hearing loss (Lin et al. 2011a) as well as the variations in age, sex, and other factor distributions across cohorts. Although many large observational studies use a 4-frequency (0.5, 1, 2, and 4 kHz) pure-tone average (PTA) > 25 decibel hearing level (dB HL) to define hearing impairment, there is varying usage of better-hearing ear (bilateral) or worse ear (unilateral) approaches (Table 8.1).

Increasing age is the strongest risk factor for hearing loss. Prevalence roughly doubles with each increasing decade of life: 27% in 60–69-year-olds, 55% in 70–79-year-olds, and 80% in adults aged 80 years or older (Lin et al. 2011a). Severity of hearing loss also increases with age such that persons aged 80 years or older are more likely to have a disabling hearing loss (46%, with moderate or greater hearing loss defined as pure tone average > 40 dB HL), as compared to 36% with mild hearing loss (Goman and Lin 2016) (Fig. 8.1).

Globally, the prevalence of age-related hearing loss increased by 26% between 2006 and 2016 (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators 2017). With a demographic shift from a relatively younger to a relatively older population, it is expected that the burden of hearing loss will continue to increase in the coming years. For example, it is projected that in the United States, by 2060, 74 million adults aged 20 years or older will have hearing loss. Of this population, older adults will bear the brunt of this burden, with 62 million adults aged 60 years or older projected to have a clinically significant hearing loss (Goman et al. 2017).

Hearing loss is more prevalent in men than in women, affecting one-third of men aged 40 years or older compared to one-fifth of women (Goman and Lin 2016). This disparity could be due to differences in risk factor profiles between men and women (e.g., noise exposure) or may be explained by hormonal differences (Meltser et al. 2008).

Table 8.1 Selected studies of hearing loss prevalence

Study	Population characteristics	Definition of hearing loss	Prevalence
Nationally Representative Studies			
Hispanic Health and Nutrition Examination Survey, 1982–1984, USA (Lee et al. 1991)	*N* = 2751 20–74 years	PTA (0.5, 1, 2 kHz) >25 dB HL in the worse ear	Mexican Americans, 11–16%; Cuban Americans, 20–23%; Puerto Ricans, 10%
National Health and Nutrition Examination Survey, 1999–2004, USA (Agrawal et al. 2008)	*N* = 5742 20–69 years 53% female	Bilateral PTA ≥ 25 dB HL; Speech frequency defined using thresholds at 0.5, 1, 2, and 4 kHz; High frequency defined using thresholds at 3, 4, and 6 kHz	Speech frequency, 8%; High frequency, 19%
National Health and Nutrition Examination Survey, 2001–2008, USA (Lin et al. 2011a)	*N* = 7490 ≥12 years	PTA (0.5, 1, 2, 4 kHz) >25 dB HL	Bilateral, 13%; Unilateral, 20%
National Health and Nutrition Examination Survey, 2001–2008, USA (Lin et al. 2011b)	*N* = 717 ≥70 years 41% female	PTA (0.5, 1, 2, 4 kHz) >25 dB HL	Bilateral, 63%; Unilateral, 12%
Korean National Health and Nutrition Examination Survey, 2010–2012, South Korea (Jun et al. 2015)	*N* = 18,650 12–97 years 50% female	PTA (0.5, 1, 2, 3, 4 kHz) ≥ 25 dB HL	Bilateral, 13%; Unilateral, 9%
National Health and Nutrition Examination Survey, 2001–2010, USA (Goman and Lin 2016)	*N* = 9648 ≥12 years	PTA (0.5, 1, 2, 4 kHz) >25 dB HL	Bilateral, 14%; Unilateral, 23%
National Health and Nutrition Examination Survey, 2011–2012, USA (Choi et al. 2018)	*N* = 522 20–69 years 47% female 100% Asian	PTA (0.5, 1, 2, 4 kHz) ≥ 25 dB HL	Bilateral, 6%; Unilateral, 7%
Population–Based Studies			
Epidemiology of Hearing Loss Study, 1993–1995, WI, USA (Cruickshanks et al. 1998)	*N* = 3753 48–92 years 58% male	PTA (0.5, 1, 2, 4 kHz) ≥ 25 dB HL in the worse ear	46%
Nord–Trøndelag (NT) Norway Audiometric Survey, 1996–1998, NT, Norway (Borchgrevink et al. 2005)	*N* = 50,723 20–101 years 53% female	Bilateral PTA (0.5, 1, 2, 4 kHz) ≥ 25 dB HL	19%
Blue Mountains Hearing Study, 1997–2000, Sydney, Australia (Chia et al. 2007)	*N* = 2431 ≥54 years 56% female	PTA (0.5, 1, 2, 4 kHz) ≥ 25 dB HL	Bilateral, 31%; Unilateral, 13%

(continued)

Table 8.1 (continued)

Study	Population characteristics	Definition of hearing loss	Prevalence
Heath, Aging and Body Composition Study (Health ABC), 1997–1998, USA (Helzner et al. 2005)	*N* = 2052 73–84 years 53% female 37% black	Speech frequency: PTA (0.5, 1, 2 kHz) > 25 dB HL in the worse ear; High frequency: PTA (2, 4, 8 kHz) > 40 dB HL in the worse ear	Speech frequency, 60%; High frequency, 77%
Beaver Dam Offspring Study, 2005–2008, WI, USA (Nash et al. 2011)	*N* = 2837 21–84 years 55% female	PTA (0.5, 1, 2, 4 kHz) > 25 dB HL in the worse ear	14%
Hispanic Community Health Study/Study of Latinos, 2008–2011, USA (Cruickshanks et al. 2015a)	*N* = 15,716 18–74 years 60% female	PTA (0.5, 1, 2, 4 kHz) > 25 dB HL	Bilateral, 8%; Worse ear, 15%

dB decibel (measure of sound intensity or volume), *dB HL* decibels hearing level, *kHz* kilohertz (measure of frequency of sound waves), *PTA* pure-tone average

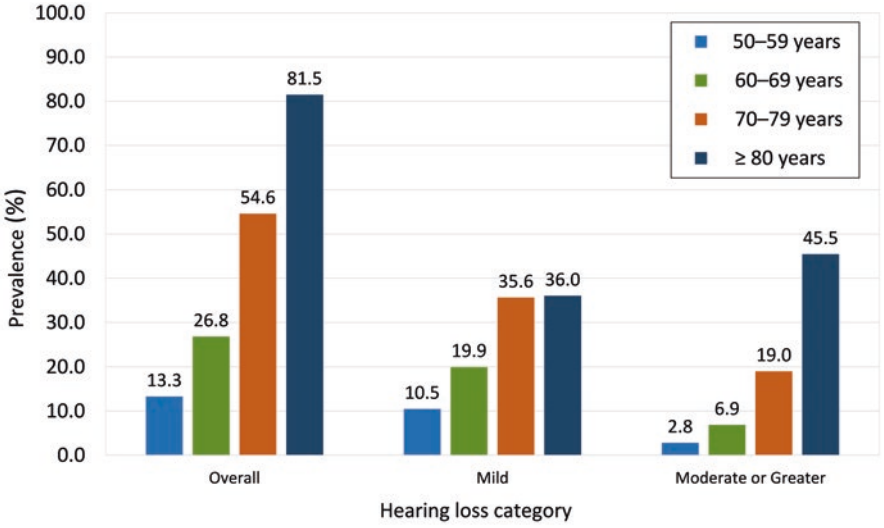

Fig. 8.1 Prevalence of hearing loss by age and severity, The National Health and Nutrition Examination Survey, United States, 2011–2010. (From data published in table form in Goman and Lin 2016)

Prevalence of hearing loss is lower across all age categories in non-Hispanic blacks compared to other race/ethnicities (Agrawal et al. 2008; Lin et al. 2011b). In a nationally representative study of US adults aged 70 years or older, the prevalence of hearing loss was 64% in non-Hispanic whites compared to 43% in non-Hispanic blacks (Lin et al. 2011b). Prevalence estimates were similar in a population-based

study of adults aged 73–84 years: 62% in whites compared to 56% in blacks (Helzner et al. 2005).

Differences in hearing loss prevalence by race/ethnicity may be due to protective effects of melanin in the inner ear (Ohlemiller et al. 2009). Consistent with this hypothesis, in 295 Hispanic adults aged 20–59, darker skin color as assessed by Fitzpatrick skin type was cross-sectionally associated with better hearing thresholds (Lin et al. 2012), although differences in skin pigmentation for other race/ethnicities have not been documented (Lin et al. 2012, 2017a). Overall prevalence of bilateral hearing loss in older Hispanic populations in the United States is similar to those of non-Hispanic whites: 65% in adults aged 70 years or older (Lin et al. 2011b). Prevalence among Asian Americans (Choi et al. 2018) is also similar to that among non-Hispanic US whites.

Characterization of temporal trends in hearing loss prevalence can provide important insight into the hearing health of a population over time. One concern when comparing the prevalence from two different time periods is that age, a very strong predictor of hearing loss, may differ between the two time periods. If so, the prevalence of hearing loss in one time period may seem greater than the prevalence of hearing loss in the other time period, only because there is a greater proportion of older adults. This concern may be overcome through age standardization (or adjustment), in order to answer the question, "If both time periods had the same age distribution, how would the prevalence of hearing loss compare?" From two studies, there is some evidence to suggest that the age-adjusted prevalence of hearing loss in older Americans is now less than for prior generations (Zhan et al. 2009; Hoffman et al. 2017). An important implication of this finding is that hearing loss may be preventable, or may at least be delayed until older age, possibly through the amelioration of modifiable risk factors. Despite this observation, however, as the absolute number of older adults continues to increase in the coming years, the burden of hearing loss will continue to rise.

8.2.3 Incidence (New Cases) of Age-Related Hearing Loss

Studies with repeated measures of hearing in a population over time are uncommon, and so estimates of the incidence (or new cases) of hearing loss are limited and come from predominantly non-Hispanic white populations (Table 8.2). Over 5 years, the risk of incident bilateral hearing loss was 18% in middle-aged populations in Great Britain (Davis et al. 1991) and Australia (Mitchell et al. 2011). The 5-year risk in a US cohort was greater (21%), although this estimate is for hearing loss in the worse ear (Cruickshanks et al. 2003); over 15 years, the risk in this cohort was 57% (Cruickshanks et al. 2015b).

Table 8.2 Selected studies of hearing loss incidence

Study name	Population characteristics	Definition of hearing loss	Incidence (new cases)
Longitudinal Study of Hearing, Great Britain and Denmark (Davis et al.1991)	Great Britain: 98 participants with an age range of 40–65 years; Denmark: 134 participants with an age range of 49–69 years	Bilateral PTA (0.5, 1, 2, 4) kHz > 25 dB HL	Great Britain: 18% over 5 years Denmark: 18% over 8 years
Epidemiology of Hearing Loss Study, USA (Cruickshanks et al. 2003, 2010, 2015b)	1636 participants; Age range, 48–92 years	Unilateral PTA (0.5, 1, 2, 4) kHz > 25 dB HL	21% over 5 years; 37% over 10 years; 57% over 15 years
Blue Mountains Hearing Study, Australia (Mitchell et al. 2011)	870 participants; Age range, 55–99 years	Bilateral PTA (0.5, 1, 2, 4) kHz > 25 dB HL	18% over 5 years

8.3 What Increases Risk for Age-Related Hearing Loss?

8.3.1 Genetic Factors Associated with Age-Related Hearing Loss

Age-related hearing loss is a complex condition with a multifactorial etiology. As such, both genetic and environmental factors likely play a role in its development. Estimated heritability indices range from 0.35 to 0.55, supporting a genetic contribution to age-related hearing loss (Gates et al. 1999; Christensen et al. 2001). There are, however, a limited number of genetic association studies of age-related hearing loss. This lack of research may be due, in part, to a lack of objective audiometric measures in large genetic population studies, and to the various phenotypes and presentations of age-related hearing loss (Van Laer et al. 2010).

Genetic factors associated with hearing loss are described in other chapters in this volume (Someya and Kim, Chap. 2; Ohlemiller and Spankovic, Chap. 3). Genes that may be related to hearing loss that have been identified from candidate gene association studies include glutathione *S*-transferase M1 (*GSTM1*), glutathione *S*-transferase T1 (*GSTT1*), grainyhead-like 2 (*GRHL2*), *KCNQ4*, and *N*-acetyltransferase 2 (*NAT2*) (Unal et al. 2005; Van Eyken et al. 2006; Van Laer et al. 2008).

Genome-wide association studies (GWAS) have the potential to identify common gene variants with small effects that are related to disease susceptibility. However, GWAS studies for age-related hearing loss are few in number. A GWAS of 1126 subjects of European descent found no significant single nucleotide polymorphism (SNP) signals (Huyghe et al. 2008). However, in a Finnish study of a founder (genetically isolated) population, the Saami, researchers found two SNPs,

rs457717 and rs161927, as reasonable candidates for further research (Van Laer et al. 2010). SNP rs161927 is located in the gene *GRM7*, which was previously implicated in another GWAS and fine-mapping study in European and Finnish cohorts; in that study, investigators found significant associations with multiple SNPs in *GRM7* (Friedman et al. 2009).

8.3.2 Noise Exposure

Noise exposure is a preventable cause of acquired hearing loss. The impact of workplace noise exposure in occupational cohorts is well documented (e.g., Lie et al. 2016). Despite governmental regulations (NIOSH 2018), an estimated 24% of hearing loss in the United States is attributable to occupational exposure (Tak and Calvert 2008). In the 2011–2012 cycle of the National Health and Nutrition Examination Survey (NHANES), 34% of adults aged 20–69 years reported exposure to noise at work, where workplace noise exposure was defined as answering "Yes" to either of the following questions: "You had to speak in a raised voice to be heard" and "You have to shout in order to be understood by someone standing 3 feet away from you" (Carroll et al. 2017). Workplace exposure was associated with two times the odds of an audiometric notch, a proxy for noise-induced hearing loss (Carroll et al. 2017). Self-reported firearm use has also been associated with high-frequency hearing loss in cross-sectional studies (Nondahl et al. 2000; Agrawal et al. 2009). In longitudinal population-based analyses, however, history of noise exposure was not associated with hearing loss incidence (Cruickshanks et al. 2010; Mitchell et al. 2011) or with faster rates of decline in hearing acuity in older adults (Lee et al. 2005).

8.3.3 Environmental Exposures

Exposure to organic solvents and heavy metals may cause hearing loss. Evidence for these relationships comes primarily from animal studies and studies of occupationally exposed workers.

In animals, hearing loss is related to exposure to several organic solvents, including trichloroethylene (Jaspers et al. 1993), xylene (Pryor et al. 1987), styrene (Pryor et al. 1987), carbon disulfide (Rebert and Beeker 1986), and toluene (Pryor et al. 1983). In 3284 men (aged 53–74) from the Copenhagen Male Study, occupational solvent exposure was associated with a relative risk of 1.4 (95% confidence interval, 1.1–1.9) for self-reported hearing impairment in males who were not exposed to noise; in men who had 5 or more years of occupational noise exposure, exposure to solvents did not confer any additional risk of hearing loss over and above the risk associated with noise exposure (Jacobsen et al. 1993). However, in smaller occupational studies, exposure to both noise and to solvents was associated with greater

risk for hearing loss than exposure to either alone. In a study of 190 printing and paint manufacturer workers, compared to workers unexposed to noise and/or solvents, workers exposed to noise and toluene concurrently had higher risk for objectively measured hearing loss than workers exposed to either noise or organic solvents alone (Morata et al. 1993). Similarly, in a longitudinal study of 542 male aviation workers in South Korea, the relative risks for objectively measured hearing loss, compared to the group with no exposure, were 4.3 for the noise-only group, 2.6 for the solvents-only group, and 8.1 for the noise and solvents combined group (Kim et al. 2005).

Heavy metals, including lead and cadmium, have also been associated with hearing loss in occupationally exposed workers (Chuang et al. 2007; Hwang et al. 2009) and a small number of population-based studies. In a nationally representative cross-sectional US study of 3698 adults aged 20–69 years, the highest (vs. lowest) quintile of blood lead was associated with a 19% increase in pure tone average, after multivariable-adjustment including occupational noise exposure (Choi et al. 2012). In 448 males from the Veterans Administration Normative Aging Study (aged 21–80 years), increased tibia lead (as a measure of cumulative lead exposure) was associated with a faster rate of change for the 4-frequency better-hearing ear PTA over a median follow-up time of 23 years, after adjustment for confounding factors, including noise exposure (Park et al. 2010).

8.3.4 Medications and Radiation

Ototoxic effects of various medications and radiation are well-documented in basic science and clinical investigations, including aminoglycoside antibiotics, quinine derivatives, and cancer therapies such as platinum chemotherapy (carboplatin, cisplatin) and radiation (Ding et al. 2012; Landier 2016). The ototoxic effects may be amplified with noise exposure (Bokemeyer et al. 1998). Incident hearing loss has been documented in patient populations of cancer survivors (Low et al. 2006; Frisina et al. 2016), although the vast majority of studies that have investigated this association have been performed in children (Landier 2016). Few population-based studies have estimated the incidence of hearing loss associated with ototoxic medication exposure using a population-based comparison group.

Salicylates, although traditionally considered an ototoxic agent (Jung et al. 1993), were found in a multivariable-adjusted cross-sectional analysis of 2052 adults aged 73–84 years (47% male, 37% African American) in the Health Aging and Body Composition study to be inversely associated with low-to-mid frequency hearing loss, particularly among black men (Helzner et al. 2005). This unexpected finding could suggest a protective effect or could be a chance finding of the study.

Analgesic use (ibuprofen, acetaminophen) was associated with increased risk of incident self-reported hearing loss in men and women in the Health Professionals Follow-up Study and in the Nurses Health Study II, respectively (Curhan et al. 2010, 2012). In a separate study, analgesic use for 6 or more years compared to less

than 1 year was associated with a 10% (for nonsteroidal anti-inflammatory use) and 9% (for acetaminophen use) increased risk of self-reported incident "hearing problem" over 20 years in the Nurses' Health Study (Lin et al. 2017b). Whether these results are due to the medication use or to residual confounding related to the underlying condition leading to regular analgesic use is unknown, although these medications result in reduced cochlear blood flow and abnormal outer hair cell function in animals (Jung et al. 1993).

8.3.5 Cardiovascular and Lifestyle Factors

Cardiovascular-related factors that may increase risk for age-related hearing loss include smoking, hypertension, and diabetes. Systemic vascular insufficiency as a result of these factors is thought to contribute to hearing loss by reducing blood supply to the cochlea (Chisolm et al. 2003). However, results investigating the association of these factors with hearing loss in population-based epidemiologic studies have been mixed.

Amoung the 1925 white participants (mean age 61 years, 67% female) enrolled in the Epidemiology of Hearing Loss Study, current smoking at baseline was associated with a 30% increased risk of incident hearing loss over 15 years (Cruickshanks et al. 2015b). A study in the Baltimore Longitudinal Study on Aging with the majority (70%) of participants younger than 60 years old at baseline, and with a similar amount of follow-up time, also estimated an approximately 30% increased risk of hearing loss over time associated with moderate or greater smoking, but this result was not statistically significant (Brant et al. 1996). Two other longitudinal studies whose study populations were older at baseline and with shorter follow-up times (approx. 5 years) found no relationship between smoking and risk of hearing impairment (Gopinath et al. 2010; Kiely et al. 2012).

Hypertension was not associated with risk of incident hearing loss in the Epidemiology of Hearing Loss Study (Cruickshanks et al. 2015b) but an analysis in the Dynamic Analyses to Optimise Ageing (DYNOPTA) cohort found that hypertension was associated with faster rates of hearing threshold increase over 11 years of follow-up in 4221 men and women aged 50–103 years (Kiely et al. 2012). When blood pressure was modeled continuously in the Baltimore Longitudinal Study on Aging, the risk of incident hearing loss increased by 32% per every 20 millimeter per mercury (mm Hg) increase in systolic blood pressure (Brant et al. 1996).

Estimates from several population-based longitudinal studies suggest a small increased risk of hearing loss associated with diabetes, but this relationship has not retained statistical significance after multivariable adjustment (Mitchell et al. 2009; Fischer et al. 2015). Although baseline diabetes status was associated with worse hearing, diabetes was not associated with longitudinal change in hearing acuity in the DYNOPTA study (Kiely et al. 2012). However, in a much larger Korean cohort of (N = 253,301) of young to middle-aged adults, baseline diabetes was associated with a 36% increased risk of hearing loss over 4 years (Kim et al. 2017). Additionally,

glycosylated hemoglobin was associated with two times the risk of incident hearing loss over 15 years in the Epidemiology of Hearing Loss Study (Cruickshanks et al. 2015b).

It is likely that cardiovascular factors confer a small increase in risk for age-related hearing loss. Microvascular damage may impact the metabolically active stria vascularis, disrupting endocochlear signal transduction; additionally, a hypoxic inner ear environment may amplify the impact of reactive oxygen species on cochlear cell death (Yamasoba et al. 2013). Although the magnitude of these effects is likely small, given the high prevalence, amelioration of these factors may have a large public health impact on the prevention of age-related hearing loss.

8.4 What Are the Consequences of Age-Related Hearing Loss?

8.4.1 How Epidemiologic Evidence Is Evaluated to Establish Cause

Epidemiology is "the study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to control of health problems" (Porta 2014, p. 95). Intrinsic to this definition is that epidemiologic research is conducted in populations, which are defined by location, time, and characteristics of the individuals in that population. Also integral to epidemiologic research is the goal of the subsequent application of that work to the prevention of disease in a population.

One of the primary goals of epidemiology is to identify factors that are associated with increased risk of a disease in a population. This allows for the identification of subgroups of the population that may be at higher risk for the disease and who may therefore benefit from intervention. The identification of risk factors in a population may also provide clues as to causes of the disease, with the ultimate goal of intervening on those factors to prevent or delay the development of the disease.

To understand epidemiology's role in identifying causes of disease, it may be helpful to first discuss other scientific approaches to determining etiology (or cause). One such approach is to study the effect of an agent on animals in a controlled laboratory experiment. However, at the end of the experiment, the results must be extrapolated from that animal to humans. Alternatively, human cell culture may be used, but at the end of the experiment the results must be extrapolated from individual cells to an entire organism.

An alternative approach to studying etiology is to conduct experiments in human populations. In epidemiology, the experimental study design is the randomized trial. Because treatment is randomly assigned, it is not linked to any patient characteristics (e.g., age, race/ethnicity, etc.), which is important because these characteristics may also be related to increased risk to the outcome. In other words, with successful

randomization, there is no bias in the assignment of treatment. Consequently, the treatment and control groups will be, on average, balanced in regard to factors related to the outcome. Therefore, any observed difference in the outcome comparing the treatment to the control group may be ascribed solely to the treatment (Gordis 2013).

Observational study designs do not have the same protection from bias as a randomized study. Any observed association may be due to several possible explanations. First, it may be that an observed association represents a true relationship between an exposure and an outcome. Second, the association may be due solely to chance. The application of biostatistical methods in the analysis and the interpretation of the data may help to evaluate this possibility. Third, the association could be due to bias. Epidemiologists consider three main sources of possible bias in any study: (1) bias due to the way in which participants are selected to participate in the study or to be included in the analysis (i.e., selection bias); (2) bias due to error in the measurement of the exposure, outcome, or other factors in the study (i.e., information bias); and (3) bias due to failure to account for other factors related to the exposure that also cause the outcome (e.g., confounding). It is the role of the investigator to evaluate the possible role of each bias in any given study, and to ensure that the inference from the study appropriately acknowledges that possible bias.

If it is believed that an observed relationship is a true relationship, how is it determined if the relationship is causal? Because of the possibility for bias in observational studies, "causal significance of an association is a matter of judgment" (US Department of Health, Education, and Welfare 1964, p. 20). The determination of cause must therefore be beyond the scope of any individual observational study and must incorporate evidence from other scientific studies in both humans and animals.

Guidelines for evaluating whether an epidemiologic association is causal have been proposed in various settings, the most famous of which are those of Sir Austin Bradford Hill (Hill 1965). Of the nine guidelines, only *temporality*, that exposure to a factor must precede the development of the outcome, is required for a factor to be a cause of a disease. Although they provide a useful framework, there is no magic checklist that allows for the definitive determination of cause (Rothman and Greenland 2005). Nevertheless, observational epidemiologic studies, when they are appropriately designed, analyzed and evaluated, do make a valuable contribution to our understanding of causes of disease in a population. Importantly, the lack of definitive proof must not lead to apathy in terms of applying epidemiologic findings for the betterment of the public's health. What must be balanced is the strength of the evidence for cause and the possible harms of avoiding public health action.

8.4.2 Communication and Quality of Life

Hearing loss adversely affects speech processing, understanding, and communication, all essential components of everyday life (Weinstein et al. 1986). Impaired communication due to hearing loss may negatively impact a person's quality of life,

defined as an "individual's perception of their position in life in the context of culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships and their relationship to salient features of their environment" (Saxena and Orley 1997, p. 263s).

Well-designed scales developed to measure quality of life specifically related to hearing, such as the Hearing Handicap for the Elderly (Weinstein et al. 1986), show a strong relationship between hearing treatment and improved hearing-specific quality of life (Ferguson et al. 2017; see Humes et al., Chap. 11). Epidemiologic studies have also sought to investigate the association of hearing loss severity and treatment with more general scales that not only focus on hearing but also measure overall quality of life.

In 2688 participants aged 53–97 years old in the Epidemiology of Hearing Loss study, increasing severity of hearing loss was cross-sectionally related to decreased function on the Mental and Physical Components of the Short Form 36 (SF-36) Health Survey (Ware and Sherbourne 1992; Dalton et al. 2003). These findings were replicated using a different scale, the Veterans RAND 12-item health status/quality of life survey (Selim et al. 2009), in a large population of Medicare beneficiaries, although hearing loss was self-reported in this study (Hawkins et al. 2012). In the Blue Mountain Hearing Study, moderate-to-severe bilateral hearing loss was also cross-sectionally associated with the Physical and Mental Components of the SF-36 (Chia et al. 2007); and in longitudinal follow-up of 432 participants free from hearing loss at baseline, incident hearing loss was associated with lower quality of life in the domains of general health and physical function (composite score) over 10 years (Gopinath et al. 2012). Data from two clinical trials (moderate-quality evidence) suggest a small positive effect of hearing loss treatment on overall quality of life (Ferguson et al. 2017).

Hearing loss may also affect quality of life for family members who do not have hearing loss themselves, but who restrict participation in activities as a consequence of the hearing loss in their significant other (Scarinci et al. 2009; see Humes et al., Chap. 11). In a systematic review, persons with communication partners who have hearing loss were found to have restricted social lives, poorer quality of life, poorer relationship satisfaction, and increased burden of communication (Kamil and Lin 2015).

8.4.3 Cognition and Mental Health

Hearing loss in older adults has been consistently linked to accelerated cognitive decline (Loughrey et al. 2018) and increased risk of incident dementia (Livingston et al. 2017) in population-based observational studies. In a meta-analysis of nine prospective studies with follow-up ranging from 6 to 18 years, hearing loss was associated with faster rates of decline in multiple cognitive domains, including

memory, processing speed and global function (Loughrey et al. 2018). Importantly, the relationship between hearing and cognitive function persists when cognitive tests that rely solely on an auditory administration are excluded (Deal et al. 2015).

Overall, hearing loss is estimated to increase risk for dementia by 94% (Livingston et al. 2017), with risk increasing as hearing loss severity increases (Gallacher et al. 2012; Deal et al. 2017a). In 639 adults aged 36–90 years enrolled in the Baltimore Longitudinal Study on Aging who were dementia-free at baseline, persons with mild hearing loss (vs. normal hearing) had 1.89 (95% confidence interval, 1.00–3.58, $N = 125$) times the risk of developing dementia over a median of 12 years of follow-up; the estimated risk for persons with moderate hearing loss (vs. normal hearing) was 3.00 (95% confidence interval, 1.43–6.30, $N = 53$) (Lin et al. 2011c).

Because so many older adults have hearing loss, prevention or treatment of hearing loss is estimated to have the greatest potential for dementia prevention compared to any other modifiable dementia risk factor. Up to 9% of dementia cases in the world could possibly be prevented with hearing treatment (Livingston et al. 2017), with the caveat that this estimate assumes a causal relationship between hearing loss and dementia (see Sect. 8.4.1).

Whether hearing loss is a cause or simply a marker of dementia is unknown. Both hearing loss and dementia may be caused by a common underlying pathology, such as vascular disease or other processes typically ascribed to "aging," or hearing loss may simply be a marker of socioeconomic disadvantage or poor health.

Alternatively, hearing loss may cause cognitive decline and dementia (Lin and Albert 2014). Hearing depends on (1) peripheral transduction and encoding of sound in the cochlea and (2) central processing of that auditory signal in the brain (brainstem, midbrain, and auditory cortex). Impaired cochlear encoding may require extra cognitive processing effort in the brain, thereby limiting effort available for encoding speech content into memory. This increase in cognitive load, also known as "effortful listening" (Tun et al. 2009), is one mechanism by which hearing may *causally* impact cognitive function (Lin and Albert 2014; Peelle and Wingfield 2016).

Additionally, neuroimaging studies suggest that hearing loss may affect the brain, even in regions outside of the primary auditory cortex. Individuals with hearing loss appear to recruit executive networks (Peelle et al. 2011) and show evidence of cross-modal plasticity between the somatosensory and auditory systems (Cardon and Sharma 2018) for compensatory processing of degraded acoustic signals. Hearing loss has also been associated with lower gray matter volume in the primary auditory cortex (Peelle et al. 2011) and with faster rates of brain atrophy over time in the right temporal lobe and whole brain (Lin et al. 2014). Finally, hearing loss may possibly cause dementia by increasing social isolation (see Sect. 8.4.5).

Although there is a robust literature about the impact of perceived (self-reported) hearing loss and mental health conditions (Chen 1994; Wallhagen et al. 1996), relatively few studies have addressed the relationship using audiometric hearing loss. In cross-sectional studies, hearing loss was associated with greater depressive symptomatology (Gopinath et al. 2009; Li et al. 2014), anxiety (Contrera et al. 2017; Cosh et al. 2018), and low emotional vitality (Contrera et al. 2016). Longitudinal population-based cohort studies using audiometric hearing data have failed to

replicate these findings (Cosh et al. 2018), although two large, multivariable-adjusted retrospective cohort studies using administrative healthcare insurance claims data found that hearing loss diagnosis was associated with a 73% increased risk of depression over 12 years (Hsu et al. 2016) and an excess of 6.9 per 100 cases of depression over 10 years (Deal et al. 2019).

8.4.4 Physical Function and Disability

Physical disability in older adults is the difference between a person's capabilities and the demands of the social and physical environments (Nagi 1976). Disability is a spectrum ranging from difficulty to dependency, and encompasses multiple domains including mobility, and higher complex functioning and basic self-care tasks. A small number of epidemiologic studies have investigated the relationship between audiometric hearing loss and disability. These studies have primarily focused on more proximal measures of disability, such as mobility or lower extremity function, but the relationship between hearing loss and more distal clinical outcomes, such as the basic self-care Activities of Daily Living (ADLs) (Katz et al. 1963) and risk of falls, has also been investigated.

Hearing loss was associated with self-reported walking limitations in a cross-sectional survey that is nationally representative of the US noninstitutionalized population (Chen et al. 2014) and in a cross-sectional analysis of 434 women aged 63–76 years enrolled in the Finnish Twin Study on Aging (Viljanen et al. 2009). In the latter study, hearing loss was also associated with objectively measured walking metrics, including slower maximal walking speed over 10 m, and lower walking endurance, defined as the number of meters covered during a 6-minute walk (Viljanen et al. 2009). Several cross-sectional studies have also reported a relationship between hearing loss and the Short Physical Performance Battery (Guralnik et al. 1994), a test that measures lower extremity function and incorporates measures of balance (static, semitandem, and tandem), chair stands (i.e., standing from a seated position with arms folded over chest) and a 4-m walk (Deal et al. 2016; Mikkola et al. 2015a).

Relationships of hearing loss with mobility and with lower extremity function have also been reported in longitudinal analyses. In the above-referenced study of the 434 women from the Finnish Twin Study, hearing loss at baseline was associated with twice the odds of developing major walking difficulty during 3 years of follow-up (Viljanen et al. 2009). In a study of 2190 older adults (mean age 74 years, 52% female, 37% African American), moderate or greater hearing loss at baseline was associated with slower gait speed and with poorer function as measured by the Short Physical Performance Battery over 11 years (Chen et al. 2015).

Hearing loss has also been cross-sectionally associated with disability with Instrumental Activities of Daily Living (IADLs), a series of higher-order, complex functioning tasks such as managing money, performing house chores, and preparing meals (Lawton and Brody 1969), and with ADL disability, including transferring in

and out of bed, eating, and dressing (Dalton et al. 2003; Chen et al. 2014). A small number of multivariable-adjusted studies evaluating the relationship between audiometric hearing loss and falls suggest a 72% to 139% increased odds of falling in persons with hearing loss compared to persons with normal hearing (Jiam et al. 2016).

Observed associations between hearing loss and physical function could be due to a common pathology affecting the peripheral auditory and vestibular systems, or to residual confounding from generalized processes, such as mitochondrial dysfunction or microvascular disease, that could affect physical and sensory function. Causal mechanisms that could explain observed associations between hearing loss and poor physical function include mediation through greater cognitive load and poorer cognitive function (Lin and Albert 2014; Peelle and Wingfield 2016), reduced awareness of the auditory environment (Rumalla et al. 2015; Campos et al. 2018), or detrimental effects on balance and postural stability (Rumalla et al. 2015).

Declines in physical function predict incident disability and mortality in older adults. The potential contribution of hearing to physical function is an understudied but promising area of future research.

8.4.5 Social Isolation and Loneliness

Social isolation and loneliness can have profound effects on the health of older adults (Holt-Lunstad et al. 2010; Perissinotto et al. 2012). Although hearing healthcare providers often intuitively recognize a link between hearing loss and increased social isolation and loneliness in their patients, these relationships have not been well described in population-based studies. Additionally, the epidemiologic studies demonstrating an association have typically used self-reported measures for both hearing loss and for social engagement outcomes (Strawbridge et al. 2000; Mikkola et al. 2015b). An important limitation in these studies is the possibility of a same-source bias: a spurious association because of correlation in the measurement error in the exposure and outcome, or because social connectedness may impact the perception of hearing loss.

Very few epidemiologic studies have evaluated the relationship between hearing loss measured objectively, such as with pure tone audiometry, and social isolation and loneliness. In one published study with audiometric hearing data, increasing severity of hearing loss (per 25 dB HL increase) was cross-sectionally associated with 3.5 times the odds of social isolation in women aged 60–69 years, but no associations were observed between hearing loss and social isolation in men or in the 70–84-year age group, and the authors relied on a composite score of several isolation-related questions pulled from multiple questionnaires, rather than using a validated measure of social isolation (Mick et al. 2014a). In a prospective study of 829 men and women aged 63–93 enrolled in the Longitudinal Aging Study Amsterdam (LASA), poorer measured speech-in-noise perception was associated with greater emotional (i.e., feeling of missing an intimate relationship), but not

social (i.e., feeling of missing a wider social network), loneliness as measured using the de Jong-Gierveld Loneliness Scale (de Jong-Gierveld and Kamphuls 1985), after adjustment for demographic and health covariates, including depressive symptoms (Pronk et al. 2011).

There is a great need for population-based research evaluating the association between hearing loss and social engagement in older adults. These studies should use objective measures of hearing loss rather than self-report in order to minimize same-source bias, and should acknowledge that social isolation and loneliness are distinct constructs, each of which may potentially be impacted by hearing loss and should be measured using validated instruments.

8.4.6 Health Resource Utilization

Health resource utilization is an important care metric for individuals, insurance providers, care providers and policymakers. It includes quantification of the cost and consumption of care services, such as hospitalization, emergency department visits, length of stay, etc. Documented associations between hearing loss and various markers of health resource utilization could potentially be explained by two, not mutually exclusive, mechanisms: (1) the association of hearing loss with costly healthcare outcomes such as dementia, depression, and falls (Deal et al. 2019) and, (2) the negative impact of hearing loss on healthcare literacy and patient–provider communication acting as a barrier to optimal patient-centered care, and contributing to increased utilization (Mick et al. 2014b; Reed et al. 2019). Notably, much of this research has been completed in administrative healthcare claims datasets which are inherently limited in capturing the exposure of hearing loss.

In a cross-sectional analysis of medical claims from the Truven Health MarketScan Research database (N = 904,750) over an 18-month period, hearing loss was associated with approximately 20% ($3587–$4657) higher total healthcare payments depending on insurance (Medicare Plus supplement, Medicare only, or dual Medicare and Medicaid) (Simpson et al. 2018). In a large claims dataset of private and Medicare Advantage enrollees from across the United States, hearing loss was associated with 46% ($22,434) higher total healthcare costs, on average, over a 10-year period (Reed et al. 2019). In the Medicare Expenditure Panel Survey (N = 34,981), hearing loss claims were associated with $392 in excess claims over a year, translating to an excess of $3.10 billion in total medical expenditures associated with hearing loss in the United States (Foley et al. 2014).

In addition to cost, health resource utilization is measured by metrics such as hospitalization and length of stay. These metrics are often used as quality of care and patient safety indicators. In a cross-sectional analysis of NHANES data, hearing loss was associated with 1.32 times the odds of any hospitalization in the previous 12 months (Genther et al. 2013). In a longitudinal analysis of 2148 participants in the Health Aging and Body Composition Study, participants with mild hearing loss (vs. normal hearing) and moderate hearing loss (vs. normal hearing) had 16%

(95% confidence interval, 1.04–1.29) and 21% (95% confidence interval, 1.06–1.38) greater risk for incident hospitalization over a median 12-year period (Genther et al. 2015). In addition to hospitalization, important measures such as length of stay, emergency department visits, and 30-day readmissions have been associated with hearing loss in claims data. Over a 10-year period, evidence of hearing loss in claims data was associated with spending 2.10 more days on average in the hospital, a 17% increase in risk of an emergency department visits, and a 44% increased risk for 30-day readmission (Reed et al. 2019).

8.4.7 Impact of Hearing Aid Treatment

Particularly in the context of cognition, there has been an effort on the part of researchers to evaluate if hearing aid use may modify the relationship between hearing loss and adverse health outcomes. Most observational studies that have addressed this question suggest that self-reported hearing aid use is associated with better cognitive function (Amieva et al. 2015; Maharani et al. 2018). However, data on key variables (e.g., years of hearing aid use, adequacy of hearing aid fitting, etc.) that would affect the success of hearing treatment, and therefore any observed association, have generally not been available in these studies (Perez and Edmonds 2012). Importantly, individuals who choose to use a hearing aid likely differ from individuals who do not wear a hearing aid. Persons who wear a hearing aid generally have higher socioeconomic status and engage in other positive health-seeking behaviors compared to persons who do not wear a hearing aid, and these factors likely also protect against cognitive decline. Consequently, results from observational studies should be interpreted with caution and cannot definitively determine whether hearing loss treatment could prevent or delay adverse health outcomes. A randomized trial will likely be required to answer this important question (Deal et al. 2017b, 2018).

8.5 Summary

Age-related hearing loss currently affects over 50% of United States adults aged 60 years and older. As the population ages, the burden of hearing loss will increase in the United States and globally. Hearing loss negatively impacts everyday communication and quality of life. The downstream consequences of age-related hearing loss from a public health perspective are only now beginning to be understood. More epidemiologic and cross-disciplinary research is needed to understand whether hearing loss can be prevented, perhaps through mitigation of modifiable factors related to cardiovascular health. Additionally, whether hearing treatment and rehabilitation can delay adverse functional outcomes, including cognitive decline and dementia, in at-risk older adults is unknown, but could have substantial clinical, social and public health impact in our aging world.

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Chapter 9
Age-Related Changes in Speech Understanding: Peripheral Versus Cognitive Influences

Sandra Gordon-Salant, Maureen J. Shader, and Arthur Wingfield

Abstract This chapter examines anatomical and physiological changes in the peripheral and central auditory system that contribute to speech understanding deficits observed in older adults, as well as how cognitive and linguistic abilities may modulate the impact of age-related limitations in hearing acuity and auditory processing. The focus is on considering auditory and cognitive mechanisms in some detail that help explain older listeners' performance on a range of speech understanding tasks that capture the challenges of every day listening conditions. In particular, the roles of working memory, linguistic context, and listening effort on representative difficult speech understanding tasks are reviewed. Emerging areas of research that address age-related differences in speech understanding performance of adults who use cochlear implants and those who are native speakers of a foreign language are also discussed, particularly in relation to the theoretical constructs presented. The chapter culminates in recommendations for several key areas of research aimed at further elucidating mechanisms that can potentially effect positive change in speech understanding outcomes for older adults.

Keywords Audibility · Cochlear implants · Cognitive aging · Lexical processing · Linguistic context · Listening effort · Phonological analysis · Speech understanding in noise · Synaptopathy · Temporal processing · Working memory

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9.1 Introduction

It has been more than 30 years since the classic report "Speech Understanding and Aging" was published by the Committee on Hearing, Bioacoustics, and Biomechanics (CHABA 1988). The report underscored the potential multifaceted influences of senescent changes in peripheral and central auditory function and cognition, as well as linguistic factors, on speech understanding performance by older adults. However, the evidence to confirm the role of many of these factors was sparse. The report inspired auditory and cognitive researchers to study these issues in greater depth by (1) using better strategies for selecting participants and stimuli, (2) collecting behavioral and electrophysiologic/imaging measures, and (3) evaluating peripheral, central, and cognitive abilities in the same participant cohort. This chapter provides a review of some of the key findings on peripheral, central, and cognitive influences on speech understanding performance by older adults, with a focus on studies published since the first volume on this subject (Gordon-Salant et al. 2010). (Readers are referred to another excellent review on this topic by Anderson et al. 2018.)

The term speech understanding is used in this chapter to refer to a listener's reception and processing of a spoken message (word, sentence, passage) and recognition of that speech signal as demonstrated by an identification response (repetition, written response, or button press). The phrase speech understanding is differentiated from discourse comprehension, which implies interpretation of the meaning of the spoken message as evidenced by, for example, responses to inferential questions about the message content.

A theoretical framework for considering the interactive roles of peripheral, central, cognitive, and linguistic factors to successful speech understanding is illustrated in Fig. 9.1. The figure shows the bottom-up processes involved in receiving the speech signal at the periphery, which entails the initial analysis of the spectral and temporal cues in the acoustic waveform. For the peripheral analysis to result in an accurate representation of the acoustic parameters of the input stimulus, the signal must be audible across the frequency spectrum and all structures comprising the peripheral auditory system must be intact. Further processing occurs in the central auditory pathway (the perceptual system), which is thought to be responsible for additional encoding of spectral and temporal features of speech in addition to binaural correlation of signals presented to the two ears. In particular, the neural pathways at this level encode rapid signal onsets and signal duration, which are critical for precise representation of the acoustic cues that distinguish one speech unit (phoneme) from another and the stress patterns of speech. Auditory object formation, defined as the ability to focus attention on a separate sound source in a complex environment, is also thought to occur at this level (Shinn-Cunningham 2008).

Most often, object formation occurs in realistic listening environments when the listener discriminates a target message from a background composed of one or more talkers. The perceptual system is also responsible for initial phonological analysis of the spectrotemporal acoustic information leading to word retrieval. The figure demonstrates that the output of the perceptual system has a feed-forward/backward loop to various linguistic operations, such as lexical access and knowledge of syntax

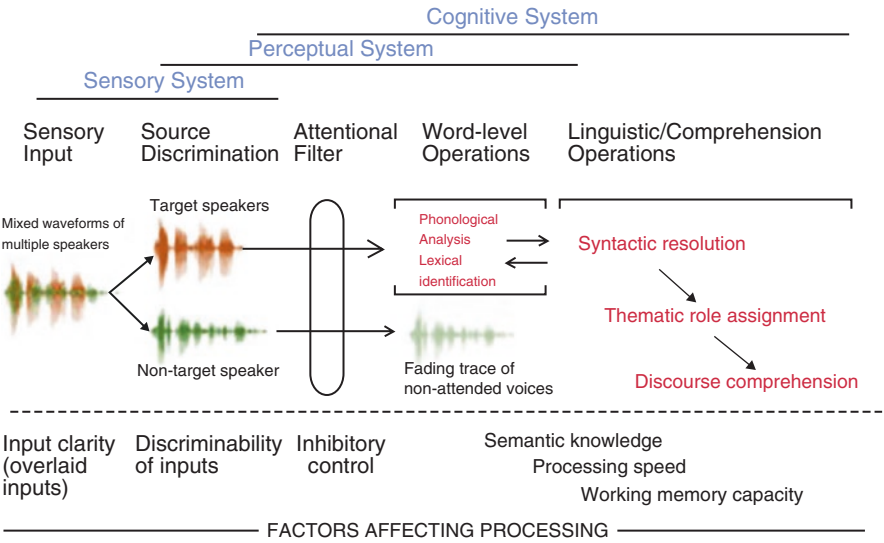

Fig. 9.1 Operations required for understanding speech at the word and sentence level, as well as discourse comprehension, as constrained to a limited capacity-processing resource system. (Adapted from Wingfield and Tun (2007), with permission from the American Academy of Audiology)

and semantics. This implies that contextual information has a direct impact on speech understanding, to the extent that the listener is proficient in the language. Various cognitive abilities, ranging from working memory and processing speed to inhibition and attention, are relevant to nearly all stages of this processing model. The processes depicted in this model must accommodate not only clean speech (i.e., speech produced by a clear talker in a quiet environment), but also degraded speech that is typical of realistic communication scenarios, such as fast or accented speech in noisy and reverberant environments.

The working premise of this chapter is that the sensory, perceptual, cognitive, and linguistic functions leading to speech understanding are constrained by a limited processing resource model. As these resources become restricted by normal age-related changes to the peripheral and central auditory systems, there is a shift in the reliance on cognitive and linguistic factors to lead to accurate speech understanding. Moreover, as age-related limitations in cognitive processes become evident, older adults must work harder, or expend more effort, in order to maintain speech understanding performance (Kahneman 1973; Pichora-Fuller et al. 2016). The demands of challenging listening situations further exacerbate these problems.

In this chapter, the foregoing concepts are used as a framework for elucidating the connections between audibility and encoding of the speech signal, cognitive and linguistic abilities, speech understanding, and aging. The chapter addresses the following questions:

(a) How do age-related changes in structures and functions of the auditory system contribute to speech understanding difficulties experienced by older listeners? (Sect. 9.2)
(b) How do age-related changes in cognitive capacity affect speech understanding and how do linguistic abilities modulate these effects? (Sect. 9.3)
(c) Do age-related differences in reliance on cognitive skills depend on the type of stimulus, availability of contextual information, stimulus ambiguity, and memory demands? (Sect. 9.4)
(d) How does motivation and effort affect speech understanding performance by older listeners in challenging speech tasks? (Sect. 9.5)
(e) Do these connections between speech understanding and increased reliance on cognitive and linguistic abilities differ between acoustic listeners (who have some residual hearing) and listeners who use cochlear implants who have no useful residual hearing but rely on an electrical representation of the speech signal that is inherently distorted? (Sect. 9.6.1)
(f) What is the nature of speech understanding performance of older adults who are nonnative speakers of English? What mechanisms account for their performance patterns? (Sect. 9.6.2)

9.2 Peripheral and Central Issues

9.2.1 Peripheral Hearing Loss

Hearing sensitivity of older adults varies widely both in degree and configuration (pattern of pure-tone thresholds across frequency) of hearing loss. This variability derives, in part, from the different etiologies that produce sensorineural hearing loss of cochlear origin among older adults, which may include age-related processes, noise exposure, ototoxicity, genetic factors, and disease. Dubno et al. (2013) developed a classification scheme of human audiometric phenotypes associated with age-related hearing loss (ARHL) that were derived from findings with animal models of ARHL of cochlear origin. The principal audiometric phenotypes are shown in Fig. 9.2. Classification of the audiograms of a large cohort of older adults (ages 50–97.5 years, $N = 1728$ audiograms) indicated that 7.5% were classified as older-normal, 22.5% were classified as metabolic (pattern associated with atrophy and degeneration of the stria vascularis, which is involved in regulating and maintaining the endocochlear potential), 18.8% were classified as sensory (pattern associated with deterioration of sensory hair cells and supporting cells in the cochlea), and 51.2% were classified as combined metabolic + sensory. Thus, the majority of older adults in this sample exhibited a relatively flat hearing loss (10–40 decibels hearing level [dB HL]) in the low frequencies and a steeply sloping hearing loss in the higher frequencies.

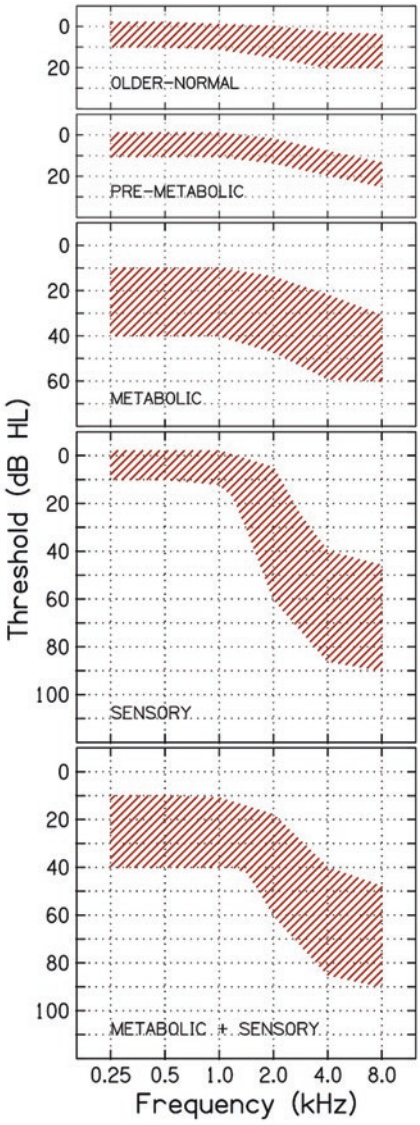

Fig. 9.2 Schematic boundaries of audiograms corresponding to five phenotypes of age-related hearing loss based on five hypothesized conditions of cochlear pathology. Red hatch marks indicate the range of audiometric thresholds that fall within each phenotype classification. Few participants had the premetabolic audiogram and this phenotype was subsequently removed. db HL, decibel hearing level. (Reproduced from Dubno et al. (2013), https://link.springer.com/journal/10162, with permission from the Association for Research in Otolaryngology)

An individual's speech understanding performance is determined by his or her hearing thresholds, as well as by the speech signal and environmental listening condition (quiet or noise). The Articulation Index (AI; ANSI, 1969; and its successor, the Speech Intelligibility Index; ANSI, 1997) is a framework for predicting speech understanding performance given the long-term average speech spectrum (LTASS), the range of speech peaks and minima, the level of background noise, and the audibility of the speech area (portion of the speech signal between 100 and 8000 Hz that is heard). The audibility can be reduced by hearing

loss and/or noise. Calculations of the AI, ranging from 0 to 1.0, are based on the effective and audible signal-to-noise ratio (SNR) of the target speech signal and background noise (if present) in each of a number of frequency bands that encompass the speech spectrum.

Humes and Dubno (2010) provide an excellent review of the principles of the AI and its application to several examples of audiograms associated with ARHL. In one example, they demonstrate that for an individual with a typical metabolic + sensory audiometric phenotype described in Sect. 9.2.1 and an input speech level of 62.5 dB SPL (the level of average conversational speech), the AI calculation is 0.53 in a quiet environment, indicating that nearly half of the speech area is inaudible. In the presence of noise (SNR = 0 dB and a spectrum comparable to that of the speech signal), the AI decreases to 0.28. These AI values can be applied to transfer functions for specific speech materials to predict the speech recognition score for that material. In this example, the listener would achieve percent correct scores in quiet of 74% and 99% for low and high-context sentences, respectively, and in noise of 39% and 75% for low and high-context sentences, respectively. Thus, the AI is a useful construct for examining the impact of audibility on speech understanding in quiet and in noise, and indeed, numerous studies have confirmed that the principal limitation in speech understanding by older listeners is reduced audibility of the speech signal associated with ARHL, particularly for speech signals that provide limited contextual information (e.g., Humes and Roberts 1990; Humes et al. 1994).

The audiometric phenotypes described above include an older-normal category, defined as exhibiting hearing thresholds that are ≤10 dB HL from 0.25 to 1.0 kHz, and ≤ 20 dB HL at audiometric frequencies up to 8 kHz. Despite good audibility of the speech signal, older adults with normal hearing often report difficulty understanding speech in noise, which has been verified in the laboratory setting (e.g., Dubno et al. 1984). There are a number of possible reasons for this observation, as discussed later in this chapter. One intriguing theory to explain this phenomenon is that aging is accompanied by a slow deterioration of ribbon synapses beneath the afferent nerve fibers that receive synaptic transmission from inner hair cells, leading to a loss of cochlear neurons (Kujawa and Liberman 2015). This type of neural deterioration, called "cochlear synaptopathy," appears to affect low spontaneous-rate, high-threshold neural fibers in mice (Kujawa and Liberman 2015). Because high-spontaneous-rate, low-threshold fibers are unaffected, hearing thresholds appear normal. However, the effect of loss of the low spontaneous-rate, high-threshold fibers becomes evident for suprathreshold signals, such as speech in noise. It has been hypothesized that the cumulative effects of cochlear synaptopathy throughout the adult lifespan result in poor temporal and spectral encoding of suprathreshold speech signals at the level of the eighth nerve (Segeyenko et al. 2013). In particular, loss of these neural fibers is thought to reduce precise encoding of rapid signal onsets and signal duration that convey specific phonetic contrasts leading to accurate word recognition.

9.2.2 Decline in Central/Temporal Processes

Aging is associated with deterioration throughout the central auditory pathway, from cochlear nucleus to auditory cortex (reviewed in Syka, Chap. 4 and Recanzone, Chap. 5). The seminal work in this area comes from animal studies showing small losses in neuron numbers in each region as well as a reduction in inhibition, both pre- and postsynaptically, at multiple levels of the central auditory nervous system (see Jayakody et al. 2018 for an extensive review). More recently, imaging studies with healthy adults have demonstrated loss of volume in regions of interest in the brain that are involved in neural networks contributing to auditory and cognitive functions, including the temporal lobe (Scahill et al. 2003), hippocampus (Braak et al. 2011), and pre-frontal cortex (Raz et al. 2001; Pfefferbaum et al. 2013). For adults with ARHL, diffuse imaging measures indicate changes in fiber density, axonal parameters, and myelination of white matter in the superior olivary complex, lateral lemniscus, and inferior colliculus (Chang et al. 2004). Additionally, structural MRI studies of older adults with ARHL show decline in gray matter volume in the auditory cortex (Peelle et al. 2011; Eckert et al. 2012). Finally, decreases in the neurotransmitters GABA and glutamate have been observed among adults with ARHL using MR spectroscopy studies (Profant et al. 2013; Gao et al. 2015). These imaging studies with humans confirm and extend many of the earlier findings observed in animal studies regarding loss of inhibitory neural transmitters and loss of neural tissue at each nucleus along the central auditory pathway. The findings also suggest that the neuroplastic changes in the brain associated with ARHL are not confined to the central auditory pathways but affect association areas as well (Peelle and Wingfield 2016).

Converging evidence indicates that these age-related structural and neurochemical alterations in the central auditory pathways affect encoding of the temporal characteristics of speech. One technique used to measure neural encoding of speech is to present a speech stimulus to listeners and to record subcortical or cortical responses to the signal. Anderson et al. (2012; see also Presacco et al. 2015) recorded brainstem responses using electroencephalography (EEG) to the speech syllable, /da/, and reported that older normal-hearing adults, ages 60–67 years, showed later peak latencies to the syllable onset compared to younger adults, ages 18–30 years. An example of age-related differences in the brainstem response to a speech syllable is illustrated in Fig. 9.3. The older adults also showed less consistent responses and lower amplitudes across the entire syllable compared to younger adults. Finally, a phase-locking factor, indicating trial-to-trial coherence, revealed better neural phase locking for younger compared to older listeners. These findings provide strong confirmation that normal aging is accompanied by both delayed neural timing and less neural precision, relative to younger adults, for processing of speech stimuli.

A subsequent study evaluated brainstem and cortical responses to speech signals presented in noise to younger and older listeners with normal hearing (Presacco et al. 2016). The frequency-following response (FFR) was measured for the speech syllable /da/ presented in quiet and in the presence of a single competing female

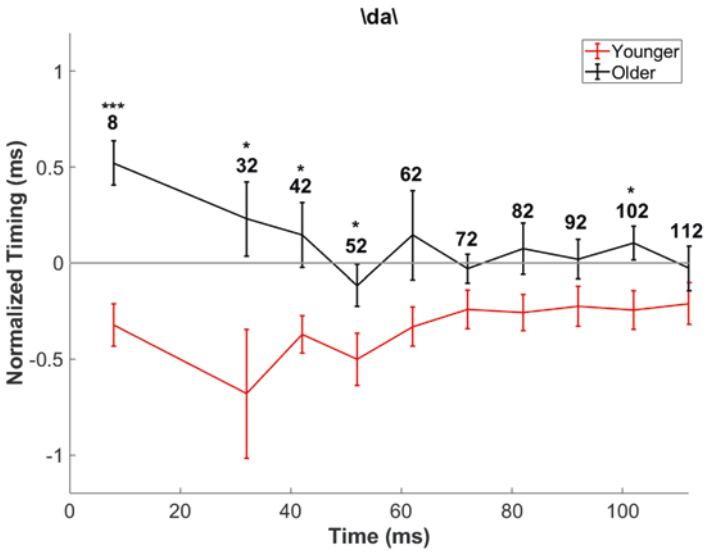

Fig. 9.3 Neural delays (mean ± 1 SE) in the aging population for the syllable /da/. The *x*-axis represents the peak analyzed for each subject, while the *y*-axis represents the normalized peak latency for each subject. To facilitate visualization of the data, peak latencies on the *y*-axis were normalized. Normalization was obtained by subtracting the expected latency from the /da/ (8, 32, 42, 52, 62 ms, etc.) from the actual response latency until 112 ms, for the transition and the steady state. Negative values indicate that the peaks were early with respect to the expected latency, positive values indicate that the peaks were late with respect to the expected latency. Older adults show a shift in neural response timing relative to the younger adults to the syllable /da/ for both the onset and transition peaks (32–52), but not for the steady state with the exception of peak 102. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$. [Adapted from Presacco et al. (2015), https://journals.lww.com/ear-hearing/pages/default.aspx, with permission from the American Auditory Society]

talker at four SNRs. In addition, neural magnetic responses were recorded in a magnetoencephalography (MEG) system while younger and older listeners with normal hearing attended to a target story in quiet or in the presence of a single competing talker at the same four SNRs as used in the EEG experiment. Midbrain FFR responses of younger adults were more robust, and responses in noise were better correlated to responses in quiet, compared to those of older adults. That is, neural encoding of periodicity in the speech envelope was less accurate among the older adults than the younger adults in the presence of competing speech, reflecting reduced temporal processing that may be associated with decreased speech understanding in noise. The MEG data of the older adults showed an overrepresentation of the cortical response, as well as a substantial decrease in the accuracy in decoding the target speech signal in the presence of the competing talker. Overall, these findings suggest that temporal processing deficits are evident at the midbrain, and compensation through neural enhancement at cortical levels may not improve accuracy in processing of speech in noise.

9.2.3 *Effects of Decline in Central Auditory Temporal Processing on Speech Understanding in Quiet*

The impact of age-related decline in the auditory system's ability to process rapid events and periodicity in the speech signal (i.e., auditory temporal processing) is manifested on multiple types of speech tasks. At the segmental level, older listeners require longer differences in the duration of acoustic cues that distinguish one speech sound from another, compared to younger listeners, as exhibited on identification functions for continua of two speech syllables differing in a single temporal cue. One example is the identification function for a *dish* to *ditch* continuum, in which older listeners require a longer silent-interval duration to shift their percept from the sibilant /ʃ/ to the affricate /tʃ/ (Gordon-Salant et al. 2008).

Similar observations have been made for other speech continua, including those that vary in voice-onset time as a cue to initial stop voicing, vowel duration as a cue to post-vocalic voicing, and transition duration as a cue to the stop-glide distinction (Gordon-Salant et al. 2008). These age-related differences in the ability to use brief temporal cues to distinguish speech segments are even greater for vocoded speech, which provides limited spectral cues, suggesting that older adults who use cochlear implants may experience additional deficits in perceiving temporal attributes of speech, beyond those observed for older acoustic listeners (Goupell et al. 2017).

Alterations in the typical rhythm, timing, and stress patterns of spoken English (i.e., sentences) also have a substantial effect on speech understanding performance of older listeners. This is thought to be another manifestation of age-related changes in the precision of neural encoding of stimulus onsets. Older adults often have difficulty understanding speech that is presented at a fast rate, usually implemented by time compression algorithms that increase the presentation rate without creating spectral distortion (e.g., Schneider et al. 2005). Listener experience with rapid speech, contextual information, and slowing at phrasal boundaries can minimize older listeners' difficulty understanding time-compressed speech in laboratory settings (Wingfield et al. 1985, 1999; Gordon-Salant and Friedman 2011). Nonetheless, most older adults, even those with normal hearing, experience disproportionate difficulty understanding naturally fast speech in everyday listening situations (Gordon-Salant et al. 2014).

Another type of temporally altered speech signal encountered in everyday life is foreign-accented speech. Nonnative speakers of English often retain the rhythm and timing pattern of their native language when learning English, and these patterns are often different from the stress-timing pattern of American English. In addition, nonnative speakers of English exhibit changes in overall stimulus duration and may insert pauses at inappropriate junctures in a spoken message. Numerous reports now indicate that older adults exhibit poorer understanding of foreign-accented speech than younger adults with comparable hearing sensitivity (Hargus Ferguson et al. 2010; Gordon-Salant et al. 2013), which may be attributed, at least in part, to difficulty following unexpected changes in stress and timing because of senescent changes in auditory temporal processing.

9.2.4 Speech Stream Segregation and Decline in Central-Temporal Processing

Central auditory temporal processing deficits have also been implicated in speech stream segregation. This refers to the ability to separate a target speech message from a competing speech message and underlies speech understanding performance in the presence of competing talkers. Older listeners have considerable difficulty understanding speech in a background of competing talkers (Tun and Wingfield 1999; Helfer and Freyman 2008; see also Gallun and Best, Chap.8).

Two types of auditory temporal processing abilities have been associated with speech stream segregation. The first is amplitude modulation detection, or the ability to detect a brief decrement in the amplitude of the temporal envelope. Temporal envelope modulation detection enables a listener to detect changes in the competing signal's temporal waveform, thus enabling the listener to take advantage of momentary increments in the SNR corresponding to dips in the waveform of the competing message. It is associated with changes in neural firing rate to the stimulus (Hopkins and Moore 2011). The second auditory temporal processing ability that may contribute to speech stream segregation is sensitivity to temporal fine structure (TFS), which refers to the relatively rapid oscillations within each frequency band of speech. TFS provides information about voice pitch (Moore 2016) and is conveyed in the neural phase-locking response to an acoustic stimulus.

Numerous investigations have examined associations between temporal-envelope amplitude modulation detection and speech understanding, as well as between TFS sensitivity and speech understanding, by younger and older adult listeners. Results have been somewhat mixed. An investigation by Füllgrabe et al. (2015) comprehensively evaluated the performance of younger and older listeners with normal hearing on a number of speech understanding, psychoacoustic, and cognitive measures. They reported a significant age effect on sentence identification performance in the presence of a two-talker competing masker, as well as on measures of temporal envelope detection and TFS sensitivity. Moreover, TFS sensitivity was highly correlated with sentence identification in noise ($r = 0.805$, $p < 0.001$), which remained after the effects of age and cognition were partialled out. These findings reinforce and extend conclusions from electrophysiology studies indicating that age-related changes in phase-locking to a speech stimulus likely contribute to difficulties in speech stream segregation and understanding speech in the presence of competing talkers (see also Sect. 9.3.2).

9.2.5 Phonological Analysis and Lexical Processing

According to the Wingfield and Tun (2007) model shown in Fig. 9.1, the subsequent stage following peripheral and central auditory system analysis of the speech signal and attention to the target speech stream is phonological analysis and lexical

processing. Phonological analysis refers to the processing of sounds (i.e., phonemes) that comprise a word in an individual's language. There is a considerable body of research investigating phonological awareness and retrieval in young children as a predictor of acquisition of spoken language and literacy success, but relatively little work has investigated the ability of older adults to conduct online phonological analysis to support word recognition. One technique used to assess online phonological analysis and word recognition is the Visual World Paradigm (Allopenna et al. 1998). The paradigm uses eye-tracking to monitor the time-course of a listener's identification of a spoken word, via eye gaze, from a limited set of competitor words represented by printed words or object pictures presented visually. The competitor stimuli are selected such that their individual phonemes differ from those of the target at varying positions in the word as the presentation of the word unfolds. For example, the target and competitor can differ in the initial position, as in the rhyming words pin versus bin, or in the final position with overlapping word onset as in pin versus pit. By monitoring eye movements to the target and competitors, the investigator can measure the listener's speed of online phonological analysis. This technique has an advantage over measuring the speed of an overt response as there are only minimal age differences in the velocity of saccadic eye movements (Ayasse et al. 2017).

Ben-David et al. (2011) surmised that this online phonological analysis would be altered in older adults compared to that in younger adults, either because of slowed processing that would limit the older listener's ability to keep up with the presentation of the target word, or because of reduced inhibition that would diminish the ability to suppress the strength of the competitor words. They compared word recognition accuracy and timing of eye movements relative to word onset for younger and older adults in conditions that varied the number of syllables, type of competitor (rhyming or word onset overlap) and presence or absence of noise, while controlling for word recognition accuracy. Age-related differences were observed in discrimination of targets from rhyming words in the presence of noise, which lasted up to 900 ms after stimulus onset. This finding suggests that older adults require longer stimulus onsets than younger adults to achieve word recognition accuracy in noise, consistent with age-related deficits in auditory temporal processing described earlier.

Accurate speech understanding also depends on the ability to identify a match between the phonemes analyzed and the listener's mental lexicon. This lexical processing is influenced by the frequency of occurrence of the spoken word in the language and the number of words in the lexicon that have overlapping phonemes with the target word, referred to as the neighborhood density. The Neighborhood Activation Model (Luce and Pisoni 1998) theorizes that word recognition accuracy is higher if the word comes from a high-frequency, low-density neighborhood than if it comes from a low-frequency, high-density neighborhood. Essentially, sparse lexical neighborhoods comprise fewer competitors to a target word that must be inhibited by the listener for accurate word retrieval.

Because older adults may have age-related changes in the ability to inhibit irrelevant information, it could be predicted that the effect of neighborhood density on word recognition accuracy would differ between younger and older listeners. Taler

et al. (2010) assessed the performance of younger and older adults with normal hearing on a sentence understanding task in which keywords varied by word frequency and neighborhood density. Compared to younger adults, older adults showed poorer accuracy overall and stronger neighborhood density effects, especially for low-frequency stimuli presented at a relatively low SNR of −3 dB. Correlation analysis between selected cognitive measures and the difference score of performance in more difficult vs. easier neighborhood density conditions revealed a significant correlation between the measure of inhibition (Stroop test—color-word naming condition) and the neighborhood density effect at the more difficult SNR presented, indicating that lower inhibitory function is associated with a large neighborhood density effect.

Helfer and Jesse (2015) extended the findings of age-related differences in lexical effects on recall of target words in sentences in the presence of a single competing talker by examining lexical effects observed not only in target stimulus recall but also in the pattern of intrusive errors from the competing speech masker. Whereas neighborhood density exerted a strong influence on target word recall by older listeners, high-frequency words in the masker were more likely to appear as incorrect target responses than low-frequency words by older listeners. Overall, the findings support those of Taler et al. (2010) and suggest that at least one factor contributing to difficulties experienced by older adults in noise is poorer access and retrieval of words from high-density lexical neighborhoods, which appears to be associated with a limited ability to inhibit the multiple irrelevant competitor's characteristic of these neighborhoods.

9.3 Cognitive Processes

9.3.1 Cognitive Change in Adult Aging

Two cognitive factors, working memory and inhibition, have been mentioned to this point in the context of adult aging, along with their importance for a full picture of speech understanding in the older adult. Working memory is defined in the cognitive literature as a limited capacity system that enables the individual to temporarily hold (store) and manipulate (process) information in immediate memory (Baddeley 2012). Inhibition refers to the ability to prevent other mental or external sources from interfering with these working memory operations (Hasher et al. 2007). Although the nature of working memory and inhibition remains an active research area in cognitive psychology, a representative characterization can be found in McCabe et al. (2010). Based on relationships and overlaps between multiple test batteries, these authors define working memory as the ability to store and manipulate information in immediate memory, and inhibition as part of a broader executive system that includes monitoring and updating performance and shifting attentional set.

A third factor associated with adult aging is a general slowing in a range of perceptual and cognitive operations (Salthouse 1996). One of several mechanisms pro-

posed to underlie the limited capacity of working memory has been a time-based model in which switching attention from processing to storage, to updating and refreshing the memory trace, are constrained by the time parameters of these processes (Barrouillet et al. 2004). A discussion of attention-based models of working memory (e.g., Cowan 1999; Engle 2002) can be found in Wilhelm et al. (2013). Readers interested on the development of current concepts of working memory resources can find a review in Wingfield (2016).

Two final points should be made. The first is that, like peripheral hearing acuity and effectiveness in central auditory processing, these cognitive fundamentals (working memory, inhibition, speed of processing) tend to decline in adult aging, but with wide differences from individual to individual. The second point is that when considering age-related changes in speech understanding, hearing and cognitive factors do more than exert independent effects on communicative success. Rather, the quality of speech understanding results from their interaction (Arlinger et al. 2009; Jerger, cited in Fabry, 2011, p. 20).

9.3.2 Cognition and Speech Understanding in Degraded and Complex Listening Environments

Over the last 10–15 years, there has been an increasing awareness by audiologists and hearing scientists of the role of cognition on measures of speech understanding (Humes et al. 2012), and a corresponding awareness by cognitive psychologists of the importance of audibility and central auditory processing to measures of cognitive processing that involve auditory presentations of stimuli. The dynamic contributions of auditory and cognitive interactions are most apparent when attempting to unravel the principal sources of speech understanding problems of older listeners in degraded and complex listening environments.

A considerable body of research has now amassed that examines the relative importance of peripheral, central, and cognitive abilities in predicting age-related decline in speech understanding performance. An exhaustive review of this literature is beyond the scope of this chapter. Nonetheless, certain trends have emerged. One trend is that measures in many cognitive domains have been associated with age-related differences in speech understanding performance in noise, even when differences in hearing sensitivity are controlled. (Note that understanding of undistorted speech in quiet is highly predictable based on signal audibility for younger and older adults, as discussed in Sect. 9.2.1). These include measures of attention/inhibition (Janse 2012), processing speed (Füllgrabe et al. 2015), executive control (Ward et al. 2017), and working memory (Füllgrabe et al. 2015). Some investigations employ a factor analysis approach in which a composite measure of cognitive performance is derived; these composite measures typically are correlated highly with speech understanding performance in noise (i.e., Füllgrabe et al. 2015).

A domain in which inhibitory ability is critical to effective functioning is in complex listening tasks such as the selection of segregated signals for attention. This is

indicated in Fig. 9.1 as an *attentional filter* that limits the ability to analyze more than one speech stream at a time. The term "cocktail party problem" was coined by Cherry (1957) to refer to one's ability to attend to a single speaker while being unaware of the content of other talkers speaking simultaneously. The fact that listeners can detect their name being spoken by a previously non-attended speaker about 30% of the time (Moray 1959) implies periodic switching of the filter to a fading echoic trace of the other voice (Broadbent 1971) or shifting the relative allocation of processing resources from one source to the other (Treisman 1969).

Consistent with arguments for an age-related inhibition deficit is the finding that older adults are more influenced by the semantic content of a to-be-ignored voice in a multiple talker situation than younger adults. For example, in a study by Tun et al. (2002) it was shown that, relative to young adults, older adults experience more interference from a second, to-be-ignored talker speaking English, than one speaking an unknown language with a similar phonological inventory (Dutch). A regression analysis conducted on these data revealed that executive control (inhibition) as measured by the Trail Making Test contributed significant variance to the ability to prevent interference from a background speaker even after accounting for hearing acuity. It is thus the case that older adults' difficulty in following a single speaker in a noisy background results from deficits at both central auditory processing and cognitive levels.

It is also the case that inhibition and working memory tend to be correlated in adult aging, and it has been suggested that working memory capacity is predictive of the effectiveness of inhibitory processes (Sörqvist et al. 2012; Lash and Wingfield 2014). Indeed, of the various cognitive domains assessed across a wide range of studies, working memory emerges consistently as a key factor contributing to speech understanding performance in noise, to include competing speech, by older adults.

9.4 Working Memory, Linguistic Context, and Speech Understanding

9.4.1 The Ease of Language Understanding Model

As indicated, working memory capacity is viewed as a limited capacity system in which, in the case of speech, the listener carries out a complex signal processing task and holds that information in a memory store for later retrieval. Rönnberg et al. (2008, 2013) have offered the Ease of Language Understanding (ELU) model as a theoretical construct for clarifying the role of the working memory system to speech understanding. The theory postulates that working memory is explicitly engaged when phonological analysis does not yield a clear signal as a result of distortions associated with signal processing devices or the presence of a noise background. Once engaged, working memory enables the listener to access stable information

held in long-term episodic memory or semantic memory to aid speech understanding. (A further discussion of the ELU model and a critical analysis can be found in Wingfield et al. 2015.)

Generally, it has been observed that individuals with high working memory capacity perform better on speech understanding tasks in noise and with fast-acting compression in hearing aids (Rudner et al. 2011; Souza and Sirow 2014), indicating that they are better able to access the information held in long-term memory or semantic memory to improve performance compared to those with low working memory capacity. Many of these prior studies evaluated adults who varied widely in age and hearing sensitivity.

Because decline in hearing sensitivity contributes to speech understanding deficits, an ideal strategy for examining possible age-related differences influencing the impact of working memory capacity on speech understanding is to evaluate listeners with normal hearing. Schurman et al. (2014) measured the SNR corresponding to 80% correct performance (SNR_{80}) for high-context and anomalous-context sentences presented in different noise maskers using an immediate recall task in which the listener immediately repeated the sentence presented. After adjusting the SNR to the level corresponding to 80% correct performance, the investigators presented the same stimuli in a delayed recall task, in which the listener recalled the sentence presented prior to the most recent sentence. Older listeners with normal hearing showed poorer SNR_{80} scores than younger adults in both sentence contexts and all masker types on the immediate recall task, although both listener groups took advantage of contextual information (i.e., better SNR_{80} scores in the high-context context compared to the anomalous-context condition). However, even after equating performance for the two age groups on the immediate recall task, substantial age effects were observed in the delayed recall task. In other words, when younger and older listeners are equated in speech recognition performance in noise, older listeners perform more poorly than younger listeners when a memory component is added to the task. These age differences were consistent for both sentence types and across masker types, as shown in Fig. 9.4. Scores on the listening (L)-SPAN test, an auditory version of the reading (R-) SPAN test (Daneman and Carpenter 1980) were highly correlated with delayed recall performance (see Fig. 9.4). The results strongly indicate that working memory is highly related to performance on everyday speech understanding tasks that involve listening in noise and waiting to respond to a target message, simulated in this study as a delayed recall task.

Working memory declines as a function of the normal aging process in the general population (Lipnicki et al. 2017), which makes it difficult to determine whether or not decline in working memory contributes to speech understanding performance independently of age. Gordon-Salant and Cole (2016) measured word and sentence understanding in noise by four groups of listeners with normal hearing: younger and older listeners with high working memory capacity and younger and older listeners with low working memory capacity. For words, younger listeners achieved lower (better) SNR scores than older listeners in both working memory groups, and listeners with high working memory capacity (both young and older) achieved lower SNR scores than those with low working memory capacity. For sentences, older

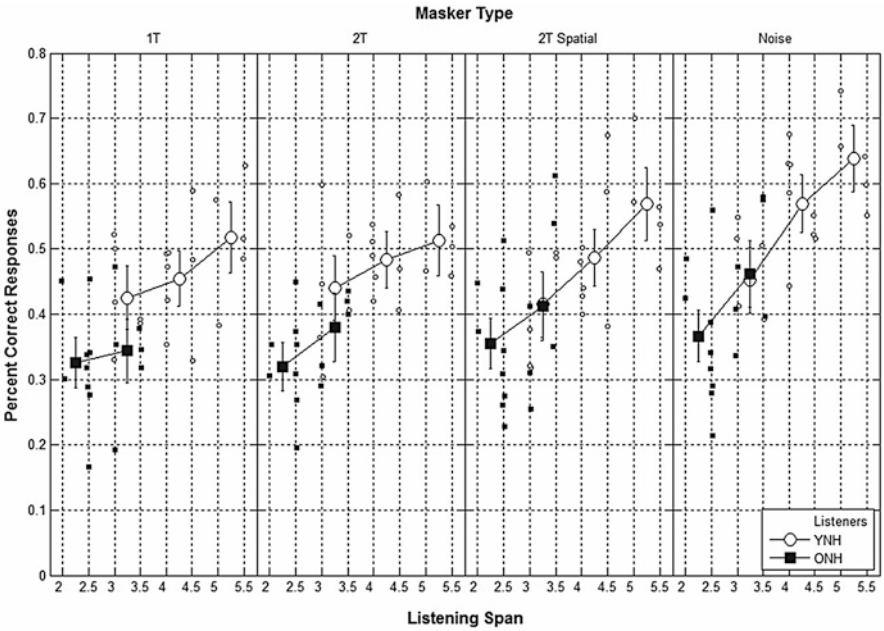

Fig. 9.4 Relationship between scores on a test of working memory (Listening Span) and percent correct sentence recognition on a delayed recall task, shown separately for four masker types [1-Talker (1 T), 2-Talker (2 T), 2-talker spatially separated (2 T-spatial) and speech spectrum noise (Noise)]. Listening Span scores are collapsed across four listening span categories (2 = scores of 2 and 2.5; 3 = scores of 3 and 3.5; 4 = scores of 4 and 4.5; 5 = scores of 5 and 5.5). Symbols represent the average percent correct scores in the delayed speech recognition task, with open circles shown for young normal-hearing listeners (YNH) and filled squares shown for older normal-hearing listeners (ONH). Individual listener data points are also plotted. Note that performance on the delayed sentence recall task is poorer for older than for younger listeners, and that scores on the L-SPAN test are highly related to performance on the delayed recall task. (Reproduced from Schurman et al. (2014), with the permission of the Acoustical Society of America)

listeners with low working memory capacity showed higher SNRs than younger listeners with low working memory capacity, but this age effect was not shown for individuals with high working memory capacity. Essentially, the older listeners with high working memory capacity were able to take considerable advantage of contextual information in sentences, which served to minimize age differences. These findings generally suggest that working memory capacity has a significant effect on speech understanding in noise, independent of listener age and hearing sensitivity. However, as some older listeners acquire both age-related hearing loss and age-related decline in working memory capacity, these individuals may be expected to experience considerable difficulties on speech understanding tasks in noise.

Although studies of context effects often contrast SNRs necessary for recognizing words heard within a constraining sentence context versus words heard in the absence of a constraining context, there is a systematic relationship between ease of

word recognition and the degree of constraint as a continuous variable. That is, it can be shown that the SNR needed to recognize a word heard within a sentence context is inversely proportional to the logarithm of its probability in that context. Such probabilities are available in published norms developed using a "cloze" procedure (Taylor 1953), in which the transitional probability of a word within a sentence context is estimated by the percentage of individuals who give that word when asked to complete a sentence with what they believe is a likely final word (Lahar et al. 2004).

Benichov et al. (2012) have shown that this relationship between ease of word recognition and the contextual probability of the word holds for both young adults and older adults with normal or impaired hearing acuity, differing only in the *y*-intercepts and steepness of the slope functions. In addition, *post hoc* regression analyses showed that while the relative contribution of hearing acuity to identification of words in noise decreased with increasing degrees of contextual support, a cognitive test battery that included working memory and processing speed remained a significant predictor of the SNR needed for identification of words heard in isolation as well as with a constraining linguistic context.

Most studies of context effects have focused on facilitative effects of a sentential context that lead up to a target word. There are, however, occasions when a poorly articulated or noise-masked word goes unrecognized until one hears the context that follows the word. Although older adults are as, or more, effective as young adults in using prior context to facilitate recognition of such words relative to their baselines for words in isolation, older adults are less effective than young adults at using a following context for retrospective recognition of an acoustically indistinct word (Wingfield et al. 1994**).** Because such retrospective recognition relies on an effective memory trace of the acoustically ambiguous region, this finding highlights an additional area in which an age-limited working memory can place the older adult at a disadvantage in speech understanding.

9.4.2 False Hearing

Older adults' facility in using a linguistic context to aid word recognition can have negative consequences if context is over-used. Such a case can occur when an acoustically indistinct word is misperceived as a word that fits the context better than the word actually uttered. Rogers et al. (2012) have found that such context-based misrecognitions are more likely to occur in older than younger adults, and that older adults are more likely than younger adults to have inappropriately high confidence in the correctness of such misrecognitions. Rogers and colleagues refer to high confidence misrecognition as "false hearing." Importantly, the higher incidence of false hearing in older adults has been shown to be largely independent of the acoustic clarity of the target word (Rogers and Wingfield 2015). This raises the likelihood that the effect is a consequence of older adults' reduced ability to inhibit high probability responses as part of a general inhibitory deficit as previously discussed in Sect. 9.3.

9.5 The Cost of Listening Effort

Although historically audiologists and hearing scientists have concentrated on hearing impaired listeners' failures in speech perception, there has been increasing attention to a cost of successful perception when faced with a degraded acoustic signal. Sometimes called an "effortfulness effect," it has been shown that the extra resources needed to successfully recognize a degraded speech signal can draw resources that would otherwise be available for encoding what has been heard in memory (Rabbitt 1991; McCoy et al. 2005) or for successful comprehension of a sentence that expresses its meaning with complex syntax (Wingfield et al. 2006).

This limited resource notion and the central role of listening effort in older (and younger) adults with impaired hearing has been encapsulated in the *Framework for Understanding Effortful Listening* (FUEL). This framework, derived from Kahneman's (1973) limited-resource model, conceptualizes successful speech understanding as dependent on a balance between the clarity of an acoustic stimulus, the task demands, and one's motivation to expend the necessary effort to meet the processing challenge (Pichora-Fuller et al. 2016). At the sentence level, effortful listening consequent to hearing loss or listening in noise, will interact in a multiplicative fashion with the linguistic complexity of the speech. To the extent that older adults have limited working memory resources, it can be seen that the detrimental consequences of listening effort on speech understanding will be differentially greater for older adults relative to young adults. Integral to the FUEL model, detrimental effects of listening effort will appear even when it can be shown that the speech itself has been correctly perceived, albeit with some effort.

Although the focus of this chapter is on recognition of a speech stimulus, a study by DeCaro et al. (2016) illustrates that when this process involves resource-demanding perceptual effort, detrimental consequences appear at the level of linguistic processing. Following a limited-resource postulate of the FUEL model, this detrimental effect will be especially marked when listeners hear sentences with syntactic structures that place a heavy demand on working memory for successful comprehension. DeCaro and colleagues tested comprehension accuracy for syntactically simple and syntactically complex sentences with three groups of listeners: young adults with normal hearing, older adults with good hearing (viz., a pure-tone average across 0.5, 1, 2, and 4 kHz < 25 dB HL), and an age-matched group of older adults with a mild-to-moderate hearing loss.

Although comprehension accuracy for syntactically simple sentences was excellent for all three participant groups, there were significantly more comprehension errors for the syntactically complex sentences, with the good-hearing older adults having more comprehension errors for these complex sentences than the young adults, and more errors still for the older adults with a mild-to-moderate hearing loss. Critically, these data were obtained even though the simpler and more complex sentences were recorded by the same speaker, had the same word-length, and were presented at the same suprathreshold, audible level. They differed only in the working memory demands they placed on the listener as the listener attempted to process the meaning of the sentence at the linguistic/cognitive level.

These data fit well within the FUEL limited-resource model (Pichora-Fuller et al. 2016). Even though the hearing-impaired older adults may have required more resources for perceptual encoding of the acoustic stimuli, the minimal working memory resources required for processing the syntactically simpler sentences left sufficient spare capacity for the excellent comprehension performance observed for these sentences. The corollary to this principle is that this same degree of perceptual effort, but now combined with the heavier resource demands required for comprehension of the complex sentences, left little spare capacity, with the resultant appearance of comprehension errors. That is, the quality of comprehension performance will reflect a balance of the resource demands imposed by the clarity of the acoustic signal, the resources required for successful processing at the linguistic level, and the level of working memory or other cognitive resources available to the participant.

The heavy resource drain of a word-by-word syntactic analysis when complex or syntactically underspecified sentences are encountered can in some cases lead listeners to a resource-conserving strategy of sampling just a few key words and inferring the meaning based on plausibility. For example, even when presented at a suprathreshold level, older adults, and especially older adults with hearing impairment, are more likely than normal-hearing young adults to respond to the sentence, "The eagle that the rabbit attacked was large" by saying that the eagle attacked the rabbit (Amichetti et al. 2016). Because we live in a plausible world, this form of experience-based shallow analysis can yield correct comprehension; it fails, however, when a sentence contains an unexpected meaning or a counterintuitive observation as can sometimes occur.

Many older adults with ARHL report an almost palpable sense of cognitive fatigue after a day of effortful listening, and several published papers have addressed the relationship between effort and fatigue, and have attempted to develop operational definitions of the two (e.g., McGarrigle et al. 2014; Wang et al. 2018). Equally important is the need to develop objective measures of processing effort that can be assessed independently from task performance (see Kuchinsky, Chap. 10).

9.6 Emerging Issues/New Directions

9.6.1 Aging, Cochlear Implants, and Speech Understanding

For individuals with more severe degrees of hearing loss for whom conventional amplification using hearing aids does not improve speech understanding, cochlear implants (CIs) may be considered as a treatment option. CIs are auditory prosthetic devices that are surgically implanted into the cochlea in order to bypass damaged inner ear structures and to directly stimulate the auditory nerve via electrical pulses. The current candidacy criteria for cochlear implantation in adults do not specify an age limit; in fact, there are cases of individuals over 100 years of age receiving a

CI. Given the incidence of hearing loss among the growing population of older adults, in addition to the introduction of more inclusive CI candidacy criteria, it is safe to assume that the number of older adults receiving CIs will continue to increase (e.g., Dillon et al. 2013). However, this trend presents an emerging issue of whether CIs are equally beneficial to older recipients as they are to younger adult CI recipients.

Cochlear implantation in individuals over 65 years old is associated with significant improvements in speech understanding scores and quality-of-life measures (Shin et al. 2000; Vermeire et al. 2005). Although CIs undoubtedly improve speech understanding ability in almost all adult CI recipients regardless of their age, post-implantation performance in older CI users may be worse when compared to younger users (Blamey et al. 2013; Sladen and Zappler 2015). However, there is conflicting evidence on the effect of advancing age on CI performance. When the amount of benefit one receives from a CI is defined by the improvement in post-implantation speech understanding scores compared to preimplantation scores, there is no impact of age on implant benefit (Pasanisi et al. 2003; UK Cochlear Implant Study Group 2004). On the other hand, because older CI candidates may have poorer pre-implantation scores than younger candidates, this could ultimately result in a substantial performance gap between younger and older CI users. Sladen and Zappler (2015) evaluated post-implantation speech understanding by measuring word and sentence recognition in quiet and in noise for an older group (mean = 70.7 years) and a younger group (mean = 39.7 years). Results showed that the older group performed significantly worse than the younger group on all speech understanding measures, with the largest group differences observed in the speech-in-noise conditions with the worst SNRs.

Given the decline in central auditory processing and cognition with age, the question remains as to whether special considerations are required for older CI recipients. If older CI users perform more poorly than younger CI users on everyday speech communication tasks, then there is a need to examine the factors that underlie this problem and identify solutions to improve performance specifically for older adults. For example, individualized device programming using a lower electrical stimulation rate for older CI users has been suggested by many clinical audiologists. and by Wolfe and Schafer (2014) and by Shader et al. (2020). Lower stimulation rates below approximately 1000 pulses per second may benefit older CI users due to declines in central auditory processing. Age-related central auditory deficits could prevent older CI users' auditory systems from processing a higher information rate of the electrical signal delivered with faster stimulation rates.

As a general rule, performance with a CI varies widely across individuals. While some individuals are only able to improve their sound awareness, many others can achieve excellent open-set speech understanding scores in quiet (Gifford et al. 2008; Holden et al. 2013). Much of the variability in speech understanding scores among CI users can be explained by factors that impact the bottom-up integrity of the signal. These factors include age at onset of severe to profound hearing loss, duration of hearing loss prior to implantation, and the etiology of the hearing loss (Blamey et al. 2013). Earlier onsets of hearing loss with prolonged periods of auditory depri-

vation prior to implantation cause neural degeneration of the spiral ganglion cells (Leake et al. 1999), which can limit the ability of the auditory nerve to accurately encode electrical signals. This would result in further degradation of the signal received by the CI user. However, even when these well-established factors are taken into account, a large amount of unexplained variability in performance remains. Cognitive factors that impact an individual's top-down processing ability could also affect speech understanding performance and contribute to this individual variability.

Age-related cognitive decline, coupled with the speech signal distortion resulting from digital signal processing algorithms incorporated in CIs, also present a potential issue for older CI users. CIs present electrical pulse trains that are amplitude modulated by the extracted envelopes derived from the acoustic input. The result is an auditory percept that is highly degraded within the spectral domain with a relatively intact temporal envelope. CI-processed speech signals present a unique form of signal degradation that substantially disrupts the bottom-up sensory input, which places a higher demand on top-down processes for successful speech understanding. Therefore, older CI users may be at a greater disadvantage compared to younger users due to age-related cognitive decline.

An age-related decline in cognitive processing has been observed in older CI users (Holden et al. 2013; Moberly et al. 2017a). Moreover, cognitive ability has been shown to correlate with speech understanding scores in CI users. Holden et al. (2013) evaluated speech understanding in 114 adult CI users and found that a composite measure of cognition was positively correlated with word recognition scores. However, when controlling for the negative effect of age on cognitive scores, there was no longer a relationship between speech understanding and cognition. This result suggested that age-related cognitive decline may have negatively impacted word recognition scores. A study by Schvartz et al. (2008) measured CI-simulated phoneme recognition in younger, middle-aged, and older normal-hearing listeners. When the acoustic stimuli were more severely degraded, younger listeners had better phoneme recognition than middle-aged and older listeners. Age of the listener and working memory ability were the primary predictors of vowel recognition performance. Working memory ability specifically has also been shown to correlate with speech understanding scores in CI users (Tao et al. 2014; Moberly et al. 2017b). The combination of age-related cognitive decline and the delivery of highly degraded speech signals presents a special challenge to older CI users.

CI users, like other individuals, can also make excellent use of linguistic context to aid word recognition (Winn 2016). As previously noted (Sect. 9.2.5), however, linguistic context can activate a large number of potential words that might reasonably fit the sentence context. Amichetti et al. (2018) evaluated the positive effects of sentence context and potential negative effects of response competition on word recognition in younger adult (mean age 22.5 years) and older adult (mean age 67.5 years) CI users. The left panel in Fig. 9.5 shows the positive effects of linguistic context on word recognition using *word-onset gating*: participants heard the first 50 ms of a recorded word, then the first 100 ms of that word, then the first 150 ms, and so on, until the word could be correctly identified (Wingfield et al. 1991;

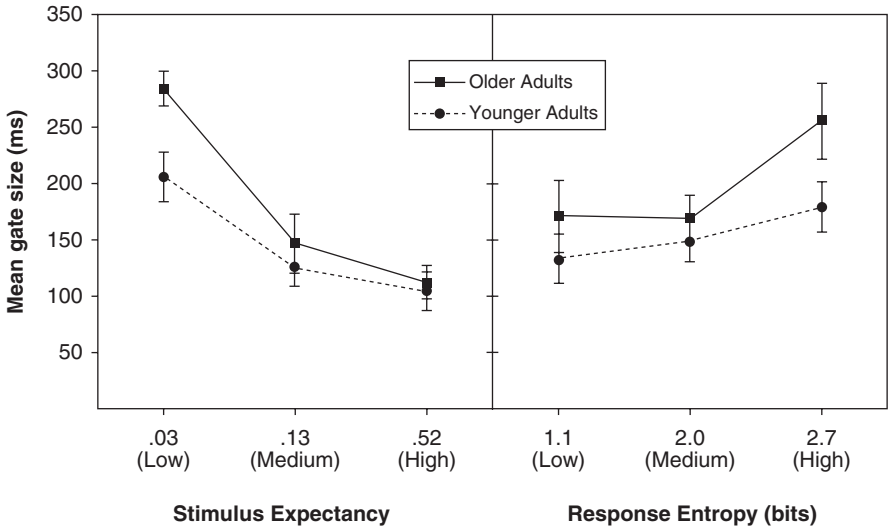

Fig. 9.5 Left panel shows mean onset gate size required for correct recognition of words heard with a low, medium, or high degree of linguistic context by younger and older adult cochlear implant users. Numbers on the abscissa are mean cloze probability values of the target words. Right panel shows mean gate size required for correct word recognition with low medium, or high degrees of response entropy for the same participants. Numbers on the abscissa are mean calculated entropy values of the target words. (Adapted from Amichetti et al. (2018), https://journals.lww.com/ear-hearing/pages/default.aspx, with the permission of the American Auditory Society)

Grosjean 1996). The target words were presented as the final words of sentences; the context of the sentences was varied in their probability of suggesting the target word based on the previously described "cloze" norms. These probabilities are shown in parentheses on the *x*-axis in the left panel of Fig. 9.5. It can be seen that for both the younger and older adult CI users, the amount of word onset information needed to correctly identify a target word decreased with increasing contextual probability of the target word, with the age difference that appears for words in a low context sentence frame reduced with medium and high contextual constraints.

As previously noted (Sect. 9.3.1), a major factor in cognitive aging is reduced efficiency in inhibiting interference from competing responses (Hasher et al. 2007). This is demonstrated in the right panel of Fig. 9.5, which shows the mean gate size needed for correct word recognition as a function of response entropy. As distinct from the stimulus probability, response entropy serves as a measure of response uncertainty, calculated as the number and probability distribution of alternative words that also fit the sentence context. This information is also available from published cloze norms (e.g., Lahar et al. 2004). High entropy occurs when all possible responses are equally likely; lower entropy occurs when some possibilities are more predictable than the others (Shannon and Weaver 1949; van Rooij and Plomp 1991). Consistent with findings for normal-hearing young and older adults (Lash et al. 2013), with high response entropy (many alternatives that could fit the sen-

tence frame) the older CI users required a larger onset gate size for word recognition than the younger adult CI users. This is the result that would be predicted from an age-related inhibition deficit.

These results show that CI users' word recognition is highly sensitive to linguistic context, with older CI users gaining a larger advantage from sentence context compared to younger CI users. However, this sensitivity to linguistic context resulted in increased interference from other potential words that also fit the semantic context, which had a negative effect on older subjects' word recognition. Therefore, older adult CI users may still be at a disadvantage compared to younger CI users, even in the presence of a robust linguistic context.

Despite the limited speech cues delivered by a CI and age-related cognitive factors, implantation has been shown to improve cognitive function in older recipients (Cosetti et al. 2016; Völter et al. 2018). Taken together, recent findings suggest that CIs provide benefit to older candidates for improving speech understanding in quiet and in noise, and for reducing age-related cognitive decline. Thus, these devices are a highly viable treatment option for older adults, but performance with CIs likely could improve further with refinement of device settings as well as with training programs that strengthen cognitive skills.

9.6.2 Language Background, Speech Understanding, and Aging

A critical and understudied population is older adults who are nonnative speakers of English. Little is known about the speech understanding abilities of this group, nor about factors that may contribute to their success or limitations in understanding English speech. Demographic data indicate that more than 13.5% of US residents are foreign born (Zong et al. 2018); roughly 12% of this immigrant population is over the age of 65 years (Batalova 2012). Similarly, 12% of older adults residing in the United States are foreign born (Batalova 2012). The majority of these foreign-born individuals speak a language other than English in the home (Camarota and Ziegler 2014), and they are likely to have varying degrees of English listening and speaking proficiency, depending on their age of arrival in the United States, years of residence in the US, age of first exposure to the second language, or other factors (Flege 2002).

The model of speech understanding and language processing presented at the beginning of this chapter (Fig. 9.1) suggests that age-related difficulties in perceiving a degraded speech signal might be compensated by an increased reliance on an individual's knowledge of the English language. But what happens when an older person's knowledge of the language is insufficient, because it was acquired as a second language later in life? Studies have reported lower recognition accuracy of spoken English by nonnative English listeners compared to native English listeners, especially in the presence of competing speech (Tamati and Pisoni 2014). Few studies, however, have attempted to examine the speech understanding abilities of older

nonnative speakers of English. It might be predicted that older non-native speakers of English exhibit much poorer recognition of English words and sentences than native speakers of English because, in addition to age-related changes in hearing sensitivity, central-temporal auditory processing, and cognitive decline, these individuals may have limited knowledge of lexical, syntactic, and semantic attributes of the English language. In the case of nonnative speakers, the phonology of the native language may be different from that of English, thus rendering the tasks of phonological analysis and lexical identification of English words even more challenging.

Gordon-Salant et al. (2019) compared word recognition performance of younger and older normal-hearing native Spanish speakers to that of younger and older normal-hearing native speakers of English. All native Spanish listeners arrived in the United States after the age of 12 years and resided in the United States for at least one year. Younger adult listeners were aged 19–33 years, and older listeners were aged 60–81 years. Stimuli were English monosyllabic words recorded by a native speaker of English and a native speaker of Spanish that were presented in quiet and noise. The results, shown in Fig. 9.6, demonstrate that the older adults for whom Spanish was their first language exhibited very poor word recognition scores in all conditions, and also showed substantial age effects (relative to young adults with Spanish as their first language) and substantial native language effects (relative to older monolingual native English-speaking listeners). Unlike the other listener groups, the older listeners whose native language was Spanish did not show large

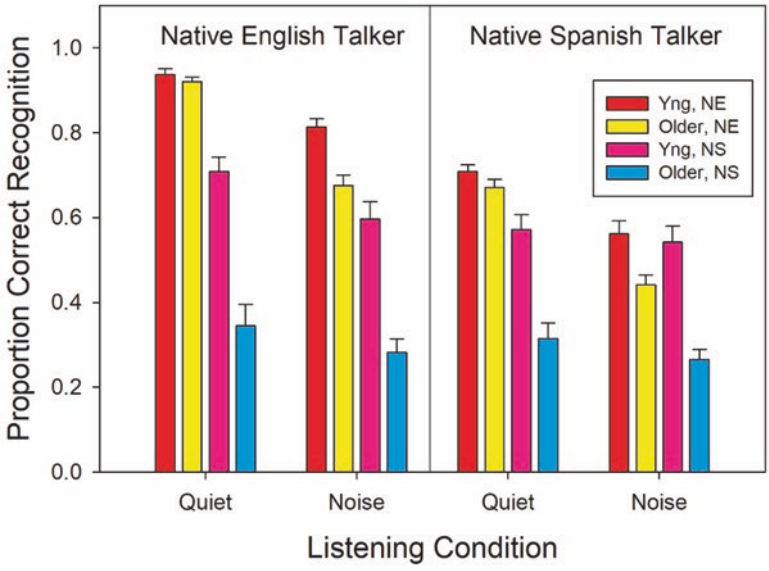

Fig. 9.6 Recognition performance for English words produced by a native English talker and a native Spanish talker in quiet and noise by four listener groups: younger native English (Yng, NE) listeners, older native English (Older, NE) listeners, younger native Spanish (Yng, NS) listeners, and older native Spanish (Older, NS) listeners. Error bars represent 1 standard error. (Adapted from Gordon-Salant et al. (2019), https://pubs.asha.org/journal/jslhr, with the permission of the American Speech, Language, and Hearing Association)

variation in performance across the speaker conditions (native English, native Spanish) or across the environmental conditions (quiet and noise).

Statistical modeling demonstrated that adding the English vocabulary score into the analyses significantly improved the model fit (relative to the model without this score), but that adding cognitive variables (i.e., working memory, processing speed, attention/inhibition) in a stepwise manner into the model did not improve the model fit. Overall, the findings suggest that when knowledge of English vocabulary is diminished, an older listener is unable to take advantage of available sources to aid lexical access and word recognition, including a quiet environment (relative to noise) and an unaccented speaker (relative to an accented speaker). Research is still needed to develop a comprehensive model of speech understanding of older nonnative listeners, including the relative importance of contextual information, word frequency and neighborhood density, education level, cognition, and numerous other factors. Such a model should also consider arguments that, even when successful, comprehension of accented speech may come at the cost of significant processing effort that may interfere with concurrent cognitive operations (Adank and Janse 2010; Van Engen and Peelle 2014).

9.7 Final Comments

The work reviewed in this chapter leads to the inevitable conclusion that older adults have difficulty understanding speech, especially in the challenging conditions encountered in everyday life that include talkers who are difficult to understand and listening environments that are distracting or serve to mask the speech signal. Because age-related hearing loss reduces audibility of key acoustic information in speech, and age-related central auditory deficits produce delayed and imprecise neural timing, the speech signal to be identified may be highly distorted.

Difficulties in speech stream segregation, as required when listening to a speech signal in a background of other talkers, compound the older adult's speech understanding task. As a result, older adults often shift their listening strategy to rely on their cognitive abilities and linguistic knowledge to understand the spoken message. They also work harder to understand degraded speech, especially because they must expend more cognitive resources to understand speech and because the pool of these resources may be somewhat limited. Among these resources, working memory ability is tightly linked to speech understanding, with attention and processing speed also related but only in certain circumstances. Nonetheless, recent findings also suggest that an older person's knowledge of the lexical, linguistic, and semantic properties of the language is a powerful mediator of the speech understanding difficulties experienced by older listeners.

Older adults who are non-native speakers of English are an important subgroup of seniors who demonstrate that limited knowledge of the English language places a heavy toll on the ability to understand spoken English by limiting access to cues that may aid speech understanding. Provision of cochlear implants to older adults with more severe hearing loss has an obvious beneficial effect on speech

understanding performance as well as on cognitive function. Future directions aimed at identifying the types of listening experiences, cognitive training paradigms, and signal enhancement devices that may preserve speech recognition and bolster cognitive reserve for seniors, regardless of native language experience and degree of hearing loss, is critical toward maintaining communicative competence among older adults.

Compliance with Ethics Requirements Sandra Gordon-Salant, Maureen J. Shader, and Arthur Wingfield declare that they have no conflicts of interest.

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Chapter 10
Aging, Hearing Loss, and Listening Effort: Imaging Studies of the Aging Listener

Stefanie E. Kuchinsky and Kenneth I. Vaden Jr.

Abstract Older adults with hearing loss often must work harder to understand speech compared to younger, normal-hearing individuals. Degraded auditory signals, sensorineural hearing loss, and age-related central nervous system declines can make listening in noise particularly effortful with increasing age. Neuroimaging studies have enhanced the understanding of the sensory, linguistic, and cognitive mechanisms that underlie speech recognition in difficult conditions and how these mechanisms change with age and hearing loss. This chapter provides an overview of neuroimaging research that has informed the current understanding of age-related changes in listening effort. In particular, this literature has revealed that older adults tend to engage more widespread activity across brain regions that support communication, such as attention and working memory. Thus, trying to understand degraded speech signals appears to increase listening-related effort and limit the mental resources available for other daily life activities. The significance of this research for clinical populations is discussed, including how neuroimaging could inform the development of targeted interventions and assessments of listening effort.

Keywords Audition · Brain activity · EEG · Executive function · Hearing impairment · MRI · Neuroimaging, Older · Older adults · PET · Speech perception · Speech recognition

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10.1 Introduction

Speech recognition is exhausting for many older adults, especially for those with hearing loss. In one poll, 85% of individuals with hearing loss reported exerting more effort when listening than their normal-hearing peers (Oticon 2016). Such listening-related effort emerges even when individuals are able to correctly recognize speech (McCoy et al. 2005; Kuchinsky et al. 2013). This suggests there may be important age- and hearing-related changes in the mechanisms that are engaged to support speech understanding in challenging environments.

Speech comprehension involves numerous interactive auditory, linguistic, and cognitive processes, particularly in adverse listening conditions (Mattys et al. 2012). These mental resources may be specific to a modality or task, such as auditory processing (i.e., so-called "domain specific"), or engaged across a variety of tasks (i.e., "domain general"), such as attention and working memory that support performance in difficult auditory as well as nonauditory tasks. Listening effort is hypothesized to increase as additional mental resources are drawn from a limited pool to meet task demands, thereby decreasing their availability for other activities (Wingfield et al. 2005). Age-related changes in the peripheral and central auditory systems that support speech recognition (Burke and Barnes 2006) may further impact their availability. For example, increased reliance on domain-general resources may explain why untreated hearing loss is associated with impaired performance even for nonauditory, cognitive abilities (see Wayne and Johnsrude 2015 for review).

Previous reviews have characterized neural changes that are associated with listening effort (Peelle 2018), aging, and sensorineural hearing loss (Peelle and Wingfield 2016). The current chapter focuses on evidence that age-related changes in the neural systems that underlie auditory, linguistic, and executive functions may explain why older adults work harder to achieve the same level of speech recognition as younger individuals (Desjardins and Doherty 2013). Neuroimaging studies will be described that assess the function of the central auditory nervous system, identify cortical activity associated with listening effort, and characterize relationships between central and peripheral auditory changes. Defining how and why individuals experience effort in difficult listening conditions may be critical for assessing and, ultimately, remediating the speech-recognition problems that they face. Thus, the chapter aims to outline how neuroimaging could be used to better characterize the severity of speech recognition difficulty; to identify suboptimal brain responses during audition; and to develop targeted, effective interventions.

10.2 Neuroimaging Methods for Auditory Research in Older Adults

A number of noninvasive neuroimaging tools have been used to investigate auditory processing in younger and older adults (see Table 10.1 for brief comparisons). These methods are broadly described here to provide context for the neuroimaging

Table 10.1 Auditory neuroimaging methods

Imaging method	Advantage	Disadvantage	Potential age-related issues
EEG: electroencephalography Summated electrical potentials from the brain measured with sensors on the scalp	Quiet; high temporal resolution	Low spatial resolution; biased sensitivity to neural population nearest to a sensor; can involve long setup	Slower oscillations; discomfort being still; background and muscle artifacts; possible atrophy-related signal changes
MEG: magnetoencephalography Summated electromagnetic fields from the brain measured with sensors near the head	Quiet; high temporal resolution; fast setup	Low spatial resolution; biased sensitivity to neural population orthogonal to sensor; typically measured in a confined environment	Slower oscillations; discomfort being still; movement artifacts; possible atrophy-related signal changes
NIRS: near infrared spectroscopy Blood oxygenation level–dependent (BOLD) signal measured using optical sensors on the scalp	Quiet; high temporal resolution in measurement sampling rate	Poor spatial resolution; slow BOLD changes limit the effective sampling rate; can involve long setup	Extracerebral signal contamination by superficial physiological changes; movement artifacts; vascular differences
fMRI: functional magnetic resonance imaging BOLD signal measured in a strong electromagnetic field.	High spatial resolution; fast setup	Loud acoustic noise; slow BOLD changes limit the effective sampling rate; spatial distortion and signal drop-out; confined setting; costly	Potential discomfort from laying position; movement artifacts; vascular differences
PET: positron emission tomography Metabolic changes in the brain measured with gamma ray detectors.	Quiet; participant-friendly environment	Exposure to ionizing radiation; low temporal resolution; costly	Potential discomfort from laying position; movement artifacts; vascular differences

studies reviewed in Sects. 10.2 through 10.9. Researchers must consider which method is best for answering their theoretical question of interest and is best suited to their population of study. Sections 10.2.1 through 10.2.3 provide a brief overview of some of these considerations, particularly as they pertain to auditory aging and hearing loss.

10.2.1 Spatial-Temporal Tradeoffs

Similar to switching the objective on a microscope, the selection of an imaging method to address a theoretical question involves a compromise between spatial and temporal sensitivity. Current techniques for in vivo human imaging are limited to

Table 10.2 Abbreviations used in this chapter

ACC	Anterior cingulate cortex
AI	Anterior insulae
BOLD	Blood oxygenation level–dependent
CRUNCH	Compensation-related utilization of neural circuits hypothesis
EEG	Electroencephalography
ELU	Ease of Language Understanding
ERP	Event-related potential
fMRI	Functional magnetic resonance imaging
HAROLD	Hemispheric asymmetry reduction in older adults
LC	Locus coeruleus
LC-NE	Locus coeruleus-norepinephrine
MEG	Magnetoencephalography
NIRS	Near-infrared spectroscopy
PASA	Posterior–anterior shift in aging
PET	Positron emission tomography
SNR	Signal-to-noise ratio
tVNS	Transcutaneous vagal nerve stimulation

studying neural populations, with more than 100,000 neurons per mm^3 of cortex (Carlo and Stevens 2013). Functional magnetic resonance imaging (fMRI; a full list of abbreviations used in this chapter is provided in Table 10.2), and positron emission tomography (PET) provide data with relatively higher spatial precision (approximately 3 mm^3), while electroencephalography (EEG) and magnetoencephalography (MEG) provide data with higher temporal resolution (typically approx. 250 Hz). Near-infrared spectroscopy (NIRS) provides data with a spatial and temporal resolution between these extremes. Because of the relative strengths and weaknesses of each method, they can produce complementary information about when and where brain activity occurs during auditory tasks.

10.2.2 Measurement Noise

At least two classes of noise must be considered when designing a neuroimaging study. The first type applies to all neuroimaging experiments: *measurement noise*. For example, MEG measurements typically cannot be collected from participants with cochlear implants because those devices generate electromagnetic interference that distorts MEG signals (cf. Johnson et al. 2012). The quality of fMRI signals depends on a static magnetic field with homogeneous strength throughout measured brain regions. Warm, moist air (e.g., in the sinuses and ear canals) or metallic dental work can cause fMRI distortion (i.e., artifacts) especially in the frontal and temporal lobes. Older adults are especially likely to have older metal

implants that can cause artifact or safety issues, as MRI was FDA-approved only in 1984 and did not gain widespread use until the 1990s.

Measurement noise is also produced by the participant. For example, blood pulsation in arteries and veins can produce aliasing effects that distort the blood oxygenation level–dependent (BOLD) signal obtained with fMRI. Physiological measurements are often collected to estimate potential influences from age-related vascular declines, particularly in methods that track blood flow (fMRI, NIRS). Another age-related source of noise may result from mobility issues that cause discomfort within the imaging setup (e.g., lying flat on an MRI or MEG bed for more than an hour). Greater head motion, blinks, and other body movements can distort or overwhelm the neural signal of interest in older adults. Furthermore, spatial normalization is typically needed to compare activity in differently shaped brains with age-related structural differences (e.g., atrophy).

10.2.3 Acoustic Noise

A second type of noise is especially problematic for studying auditory functions with fMRI: the *acoustic noise* associated with image acquisition. Neuroimaging data are collected silently during auditory experiments with most imaging modalities, except for fMRI. The acquisition of brain images in the MRI scanner can generate noise levels above 100 dB SPL. Even with the attenuation provided by insert earphones, a speech task performed during a continuous MRI acquisition will effectively become a speech-in-noise task. Auditory cortex is also flooded with activity in response to scan-acquisition noise, diminishing the effects of acoustic stimuli on activity. Special scan sequences have been used to circumvent these issues to some extent (see Peelle 2014 for a review).

10.3 Theories of Effortful Listening

The Framework for Understanding Effortful Listening (Pichora-Fuller et al. 2016) defines effort in terms of how mental resources are allocated to a task in a goal-directed fashion, such as listening for the purpose of understanding. Following from this and other capacity-limited models of attention (Kahneman 1973), the level of effort that one expends is driven by the demands of the task, the individual's resource capacity, as well as his or her motivation to apply his or her limited resources to meet these demands. For example, individuals with poorer working memory may be less able to recruit memory-related, cognitive resources in noisy listening conditions (Rönnberg et al. 2013). In addition, individuals may not engage in effortful listening if the costs of allocating resources to speech understanding outweigh their potential benefits in terms of intelligibility (Eckert et al. 2016).

An inverted U-shaped function has been proposed to relate task demands to performance and effort (Fig. 10.1), such that effort peaks in moderately difficult conditions and is relatively lower for both easier conditions and impossibly hard conditions that cause people to give up. Of particular note is the dissociation between effort (black, solid line) and performance (gray, dotted line), such that high levels of performance can be associated with moderate to low levels of effort. Indeed, previous research suggests that significant changes in effort can occur even when individuals can correctly recognize speech stimuli (McCoy et al. 2005; Kuchinsky et al. 2013). This nonlinear pattern linking listening demands, effort, and performance has been observed in behavioral, pupillometry, and neuroimaging studies (e.g., Wild et al. 2012; Ohlenforst et al. 2017).

The pattern shown in Fig. 10.1 suggests counterintuitively that interventions that improve speech intelligibility, such as hearing aids or speech-perception training, could in some circumstances yield an increase in listening effort. If individuals' resource capacities are overwhelmed by the demands of a challenging listening situation, they are more likely to give up and exhibit low effort and low performance (Fig. 10.1, red star, leftmost part of the plot; Ohlenforst et al. 2017; Ayasse and Wingfield 2018). Effective interventions may increase the availability of spare mental resources that can be allocated to support improvements in speech-understanding performance (Fig. 10.1, yellow star, middle part of the plot). As intelligibility approaches ceiling levels, listening may ultimately be less dependent on the

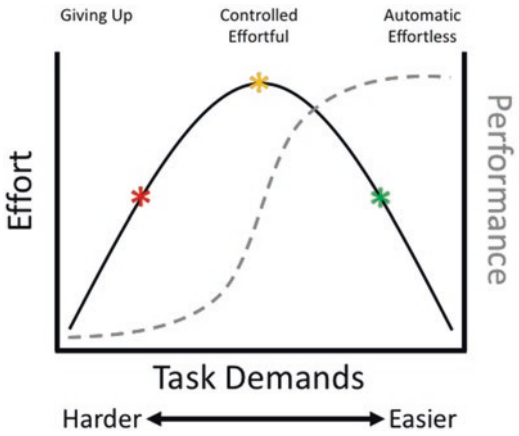

Fig. 10.1 Effort and performance are predicted to change nonlinearly as task demands increase. In the most difficult listening conditions where speech recognition is poor, individuals may disengage listening effort (red star). When task demands are more moderate, individuals may commit greater effort and increase the allocation of resources to improve speech recognition performance (yellow star). When the task demands become relatively easy, individuals are predicted to exert less effort and allocate fewer resources during speech recognition (green star). Thus, listening effort (black, solid line) and performance (gray, dashed line) are not collinear: large changes in effort may occur without observable differences in task performance. Such changes in effort and performance may be observed as a result of either exogenous changes in task conditions or endogenous changes following learning and training-related improvements

engagement of these resources and proceed more "automatically" on the basis of sensory and perceptual input (Fig. 10.1, green star, rightmost part of plot). In this way, interventions that improve intelligibility from very low to moderate levels may be associated with an initial *increase* in effort (from the red to yellow star). Further improvements from moderate to high levels of intelligibility may be associated with a *decrease* in effort (from the yellow to green star). Indeed, research suggests that intervention outcomes may be more comprehensively characterized by including measures of both speech-recognition performance and listening effort (Humes 1999).

Some studies have observed that effort asymptotes with increasingly easy listening conditions (Cabestrero et al. 2009), rather than falling off as depicted in Fig. 10.1. The exact shape of the function is likely to be affected by factors that include motivation, cognitive resources, and perceptual abilities (Peelle 2018), all of which may change with age and hearing loss. For example, aging has been hypothesized to involve a transition from automatic (effortless) to controlled (effortful) processing of sound stimuli, as evidenced by changes in the preattentive mismatch negativity component of the EEG signal (Alain et al. 2004). The role of aging and hearing loss on the upregulation of controlled processes will be discussed in more detail, particularly throughout Sect. 10.7.

Neuroimaging methods can be used to evaluate the mechanisms that drive the apparent nonlinear relationship between effort and performance. Experimental manipulations that affect speech intelligibility have been observed to produce such patterns in brain activity (Wild et al. 2012). Figure 10.2 shows an example of this nonlinearity. Cingulo-opercular activity, which appears to support performance monitoring and adaptive control (see Sect. 10.7.2.3), was lower in conditions with either high or low speech intelligibility as a result of filtering the speech. Activity was highest in moderately difficult task conditions, in which speech recognition was neither at floor nor ceiling levels of accuracy (Vaden et al. 2017). This pattern echoes the effects of training and expertise, in which individuals initially upregulate neural activity when learning a novel, difficult task and, with further experience and as the task becomes more automatic, exhibit a reduction in that activity (Doyon et al. 2002; Brefczynski-Lewis et al. 2007).

In frontal regions that support domain-general executive functions, the type of acoustic degradation does not appear to impact the nonlinear relationship between intelligibility and neural activity. In a study with younger adults, Davis and Johnsrude (2003) observed that moderately degraded speech yielded a larger neural response compared to both unprocessed and highly degraded speech. However, this inverse U-shaped pattern of activity was impacted only by the type of degradation (i.e., speech in noise, segmented speech, vocoded speech) within regions of temporal cortex that support domain-specific, auditory processing, and not within regions of the opercular portion of the left inferior frontal gyrus that support domain-general performance monitoring.

Further evidence that cingulo-opercular activity may reflect listening effort comes from an observed increase in activity for acoustically distorted sentences, but only when listeners have been directed to perform a task with those stimuli (Wild et al. 2012). Activity in cingulo-opercular regions increases during challenging task

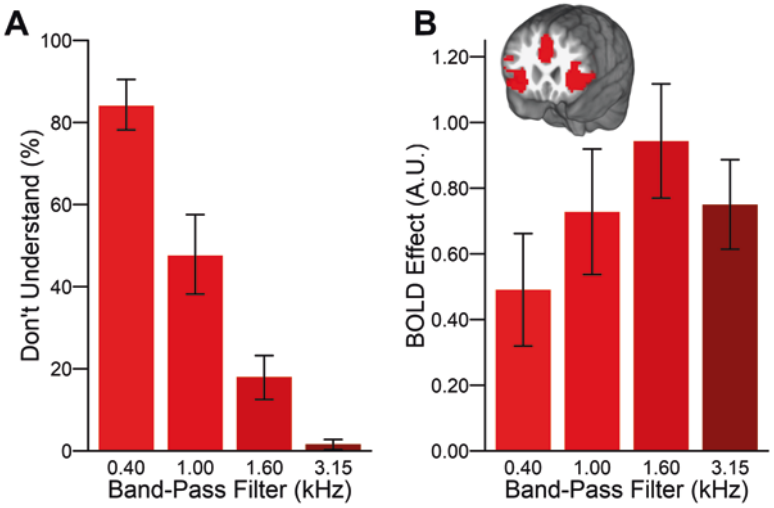

Fig. 10.2 During an fMRI study, 20 normal-hearing, younger adults listened to band-pass filtered (BPF) word recordings, with a lower cutoff frequency = 0.25 kHz and upper cutoff frequencies = 0.4, 1, 1.6, or 3.15 kHz. Participants were instructed to respond by button-press to each individual word presentation, indicating when they did not understand what was said. (**A**) As predicted, speech intelligibility increased linearly with broader BPF conditions. (**B**) Cingulo-opercular regions of the brain (shown in red) were most active (highest BOLD contrast compared to resting baseline) at moderate levels of task difficulty, i.e., percent of "don't understand" responses were not at ceiling or floor levels. Together, these results illustrate a linear relationship between listening task difficulty and performance and a nonlinear pattern of cingulo-opercular activity that is consistent with predictions for listening effort. (**A** and **B** based on data published in Vaden et al. 2017)

conditions across varied cognitive and sensory task domains (Dosenbach et al. 2006; Petersen and Posner 2012), consistent with an executive function that allocates attention, working memory, and other cognitive resources to support performance. In particular, cingulo-opercular network activity appears to recruit additional executive functions via the upregulation of frontal-parietal regions; a drop in the signal-to-noise ratio (SNR) increases the need to inhibit irrelevant information to prevent speech recognition errors. Mechanistic accounts of cognitive effort have detailed the role of the anterior insulae (AI) and dorsal anterior cingulate cortex (ACC) within the cingulo-opercular network and dorsolateral prefrontal cortex in supporting these functions (for a detailed account, see Shenhav et al. 2017). For example, the AI may signal salient shifts in the environment, serving as a link between the ventral attention salience-detection network and the cingulo-opercular performance monitoring network (Eckert et al. 2009). In challenging conditions with heightened demands for cognitive resources, the ACC is proposed to recruit cognitive control functions in lateral prefrontal regions to support correct performance (Kerns et al. 2004), for example enhancing auditory signal processing via functionally connected frontal and sensory systems (Crottaz-Herbette and Menon 2006). These findings are consistent with the hypothesis that listening effort involves

the adaptive engagement of attention and sensory neural systems in goal-directed listening tasks. Section 10.4 provides an overview of how these systems vary with age-related changes in speech recognition and listening effort.

10.4 Theories of Age-Related Changes in Effortful Listening

There appear to be differences in the extent to which older adults engage sensory and attention-related systems to support demanding tasks in any domain (e.g., Nielson et al. 2002; Grady et al. 2006). Older adults have generally been observed to upregulate more distributed cortical regions to perform challenging tasks compared to younger adults. Indicative of this pattern being linked to age-related increases in effort is that once the subjective difficulty of task conditions is matched across age groups, more similar patterns of activity are likely to be observed (Schneider-Garces et al. 2010).

Age-related changes in neural activity have been described in a number of models, including the posterior–anterior shift in aging (PASA; Davis et al. 2008), the compensation-related utilization of neural circuits hypothesis (CRUNCH; Reuter-Lorenz and Cappell 2008), and the hemispheric asymmetry reduction in older adults (HAROLD; Cabeza 2002). Broadly, neuroimaging studies supporting these models have observed that older adults engage more widespread regions of cortex at lower levels of task load than younger adults. More extensive regional activity may be indicative of age-related declines in the ability to inhibit irrelevant cortical processing (i.e., de-differentiation, often with poor performance) and/or greater recruitment of additional processes to compensate for age-related declines (often with good performance; for a review see Wingfield and Grossman 2006).

Age-related differences in the neural systems that support speech recognition have been observed to follow a similar pattern: older adults engage more diffuse sensory and attention-related neural regions during speech recognition compared to younger adults (Eckert et al. 2008; Wong et al. 2009). However, not all additional neural activity benefits task performance. While greater engagement of frontal attention regions has been linked to improved word recognition performance in older adults, age-related changes in visual cortex activity (particularly in the absence of relevant visual information; Kuchinsky et al. 2012) may be associated with an overall higher likelihood of recognition errors (Vaden et al. 2015). Observations of frontal cortex up-regulation are consistent with behavioral and pupillometry evidence for increased listening effort with aging and sensorineural hearing loss (Pichora-Fuller et al. 1995; Zekveld et al. 2011).

Potentially driving the need for functional reorganization are the widespread age-related changes in brain structure, including across regions that support sensory and executive functioning (Good et al. 2001; Resnick et al. 2003). Furthermore, hearing loss has been associated with declines in total brain volume as well as within auditory cortex (Lin et al. 2014). Given that adults wait approximately 10 years from suspecting hearing loss to being fit with hearing aids (Davis et al. 2007), such

pervasive changes in brain structure may be critical to consider in the development of effective interventions. For example, research suggests a link between more extensive structural atrophy in older adults and greater functional neuroplasticity in surrounding cortical regions (Greenwood 2007). This work suggests that interventions may be most effective when they promote the engagement of intact neural systems to compensate for age-related structural changes in other systems.

Neuroimaging research thus adds to the understanding of how older adults compensate in the face of changes in auditory and cognitive functions. Sections 10.5 through 10.7 provide an overview of neuroimaging studies that have investigated age-related differences in the engagement of auditory, linguistic, and cognitive processing in difficult listening conditions.

10.5 Neuroimaging Studies of the Impact of Aging on Auditory Processing

Age-related changes occur throughout the auditory periphery and central nervous system, altering the magnitude of auditory cortex activity in response to acoustic stimuli and potentially distorting speech representations encoded in brain activity. Auditory cortex activity (as measured by the BOLD response) often decreases in response to speech when intelligibility is reduced (Fig. 10.3, red regions), whether due to lower presentation levels or signal distortions (Kuchinsky et al. 2012; Erb et al. 2013). Given that older adults demonstrate poorer recognition of audible speech in noise compared to younger adults (Dubno et al. 1984), speech-related activity in auditory cortex should be expected to change with age. Indeed, neuroimaging studies have shown that auditory cortex activity changes with age and sensorineural hearing loss (Peelle et al. 2011; Profant et al. 2015).

Functional neuroplasticity studies also suggest that speech encoding is less accurate in auditory cortex for older adults (Du et al. 2016; Presacco et al. 2016). Du et al. (2016) found that BOLD activity patterns measured with fMRI could not be used to correctly classify a presented speech signal within auditory cortex in older adults, unlike younger adults. Instead, frontal cortex activity accurately decoded speech stimuli in older adults, reflecting either a proposed speech-motor prediction or other frontal mechanism to support speech recognition performance. Evidence of compensatory changes have also been observed within auditory- and speech-related cortex. In an MEG study, more extensive medial temporal cortex activity was observed for older adults who exhibited reduced activity in primary auditory cortex (Brodbeck et al. 2018).

As suggested by Greenwood (2007) and others, functional neuroplasticity may be driven by structural atrophy. Evidence of structural changes has been observed in the auditory cortex of older adults and appears related to the compensatory engagement of frontal cortex regions during difficult speech recognition tasks (Eckert et al. 2008; Harris et al. 2009). In particular, gray matter volume appears to decrease in auditory cortex for older adults with higher pure-tone thresholds (Peelle et al. 2011; Eckert et al. 2012). Structural changes in auditory cortex may result

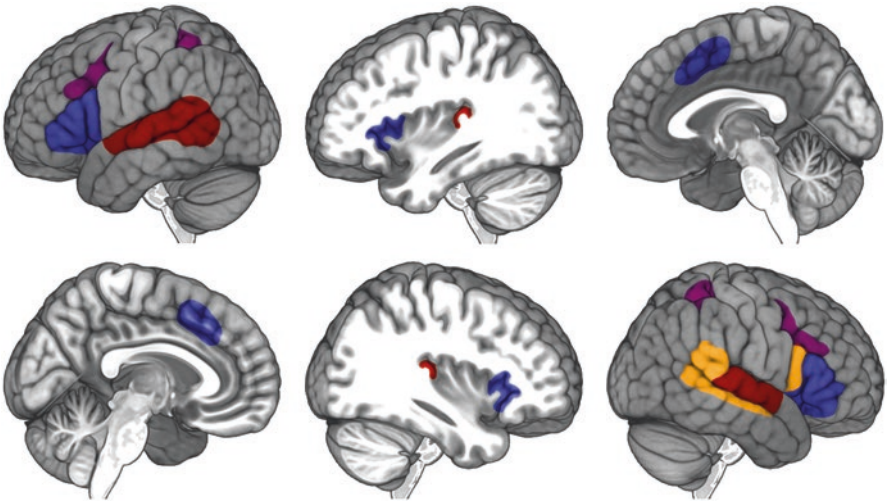

Fig. 10.3 Cortical sensory and attention networks that are often active during challenging listening tasks are illustrated on a template brain. The top row shows a sagittal series of slices from the left hemisphere, cutting from the lateral/outside to the midline of the brain. The bottom row shows sagittal cuts for the right hemisphere from the midline outward. Primary and secondary auditory cortex are shown in red colored regions, which are typically more extensive in the left hemisphere during speech recognition (Sect. 10.5). The ventral attention network is shown in yellow and is defined by a robust response to salient acoustic events and more extensive activity in the right hemisphere (Sect. 10.7.2.1). The dorsal-attention/fronto-parietal network, which is important for selective attention (Sect. 10.7.2.2), is shown in violet. In blue is the cingulo-opercular network, which is involved in an adaptive control function during challenging speech recognition tasks (Sect. 10.7.2.3). Activity within these networks may overlap, although each is depicted in adjacent brain regions for clarity of presentation

from age-related hearing loss gradually weakening input to auditory cortex over the course of decades. Compounding problems for older adults, poor vascular health also appears to negatively impact cochlear function (Pauler et al. 1988; Gates and Mills 2005) and may provide a common-cause explanation for observed associations between age-related hearing loss and structural MRI evidence of cerebral small vessel disease (i.e., white matter hyperintensities indicative of decreased blood flow; Eckert et al. 2013) as well as whole-brain atrophy (Lin et al. 2014). Because the cortex and cochlea are supplied blood through relatively tiny vessels, both could be affected by vascular condition.

10.6 Neuroimaging Studies of the Impact of Aging on Linguistic Processing

When speech is degraded, for example in the presence of background noise or hearing loss, individuals are less able to rely solely on acoustic cues to understand speech. Higher order functions may be brought online to maintain speech recognition

performance. For example, linguistic knowledge is typically well preserved with aging (for a review, see Wingfield and Stine-Morrow 2000). However, other cognitive resources such as processing speed and executive function decline with age (see Gordon-Salant et al., Chap. 9). Thus, neuroimaging may provide insight into the compensatory mechanisms available to support performance in difficult listening tasks.

Having well-instantiated representations of the phonological, lexical, syntactic, and semantic patterns in one's language can reduce uncertainty by limiting potential candidates for a word, phrase, or sentence that was heard. For example, a listener is more likely to hear the last word in the sentence "I like my coffee with cream and ___" as "sugar" (rather than "cougar" or "zugar"), because he or she expects a semantically appropriate noun that is a real word in the English language. The use of contextual information to build expectancies during sentence comprehension has been well studied in terms of the N400 event-related potential (ERP) in EEG research (Kutas and Federmeier 2011) as well as related components in MEG and optical imaging studies (Pylkkänen and Marantz 2003; Tse et al. 2007). The N400 measure has been observed to change with age, becoming smaller, later peaking, and more variable (Kutas and Iragui 1998). Thus, older adults' tendency to rely more on sentence context and linguistic knowledge to support speech recognition than younger adults (Saija et al. 2014) may come at the cost of greater processing demands, and ultimately listening effort (Pichora-Fuller et al. 1995).

Age-related differences in linguistic processing have also been observed using fMRI. In a study by Peelle et al. (2010), younger and older adults were highly accurate in parsing syntactically simple and complex sentences (i.e., subject-relative vs. object-relative). However compared to younger adults, older adults exhibited lower activity in language-related regions, specifically the left inferior frontal gyrus, in response to complex versus simple sentences, and higher activity in prefrontal regions. This work suggests that older adults can compensate for age-related changes in linguistic processing by coordinating activity across multiple regions involved in linguistic processing.

10.7 Neuroimaging Studies of the Impact of Aging on Executive Functioning

10.7.1 Working Memory

Engagement of other cognitive resources may also support speech understanding in highly challenging listening conditions. In particular, the Ease of Language Understanding (ELU) model posits that resolving mismatches between degraded auditory input and phonological representations requires the use of working memory and therefore evokes listening effort (Rönnberg et al. 2013). Indeed, age-related changes in the N400 response are particularly pronounced for those with lower working memory capacity (Federmeier and Kutas 2005).

Grossman et al. (2002) observed that older adults with good speech recognition performance exhibited increased activity within working-memory brain regions during task performance, such that their accuracy was equivalent to that of younger adults. This suggests that working memory can help mitigate potential declines in performance when speech recognition is difficult. Yet there appear to be limits on the extent to which this particular executive function alone can overcome age-related deficits in speech understanding. In an EEG study of older adults, Petersen et al. (2015) examined power in the alpha band, which has been associated with working memory processes that facilitate the inhibition of task-irrelevant information. Greater alpha power was observed at low and moderate levels of working memory load and background noise. However, even though stimuli were audible, alpha power decreased with hearing loss under the highest load and noise conditions. Thus, working memory may be less engaged in especially adverse listening conditions, when this executive function alone is insufficient to compensate for the increasing challenge of speech understanding.

10.7.2 Attention

Neuroimaging studies of speech recognition in difficult conditions demonstrate that reducing intelligibility typically results in lower activity in auditory cortex and higher activity in large-scale attention systems in frontal and parietal cortex (Peelle 2018). These systems are thought to (1) redirect attention to loud or salient sounds, (2) selectively enhance or suppress the processing of sounds, and (3) optimize performance through adjustments in behavior and the allocation of cognitive resources. Those functions map onto distinct cortical networks (Dosenbach et al. 2007) and differ for younger and older adults during the performance of speech recognition tasks (Erb and Obleser 2013; Vaden et al. 2015). These networks appear to affect speech recognition (Vaden et al. 2013), consistent with a growing literature showing how these networks influence behavior (Mišić and Sporns 2016). These systems are conventionally referred to as *attention networks*, although each constituent brain region potentially performs a unique function to support perception and performance (Eckert et al. 2016). An overview of these networks is shown in Fig. 10.3.

10.7.2.1 Orienting

Abrupt and salient acoustic changes (e.g., introducing noise after a prolonged rest period) often trigger strong neural activation across the right AI and inferior frontal operculum, right temporo-parietal junction, and right superior temporal sulcus. These regions make up a “ventral attention” network (Corbetta and Shulman 2002; Fox et al. 2005; Fig. 10.3, yellow regions). Their activation is known as an orienting response that redirects the focus of attention to a potentially important stimulus, which can include sounds that warn of danger. fMRI and EEG studies have shown

that the responsiveness of the ventral attention network to exogenous cues may signal for endogenous shifts of attention to support auditory task performance (Larson and Lee 2013). Sections 10.7.2.2 and 10.7.2.3 describe these compensatory networks in greater detail.

Age-related changes in orienting responses have been observed in terms of differences in BOLD activation during transitions between listening and rest blocks. Activity has been observed to be more bilateral and extensive across primary sensory cortex for older adults (Kuchinsky et al. 2016). This may reflect a central gain to offset peripheral changes (e.g., age-related hearing loss) that might otherwise weaken sensory input for salient stimuli that often serve to warn of danger (e.g., cars honking, dog barking).

10.7.2.2 Selective Attention

Attention-related modulation or filtering of irrelevant stimuli is critical when a listener needs to focus on speech information from a specific talker while ignoring competing talkers or noise. Selective attention is associated with changes in brain activity that can amplify or enhance some speech representations, while suppressing distracting information. Intensity, spatial location, pitch, and voice cues can facilitate a perceived separation of auditory signals into distinct sources that can be processed more extensively based on their goal-relevance. Thus, acoustic similarity between targets and maskers lead to failures of source separation and selection (Shinn-Cunningham 2008). Bilateral activity across frontal and parietal cortex referred to collectively as the "dorsal attention" or fronto-parietal network (Fig. 10.3, violet regions) is upregulated during selective attention to speech (Eckert et al. 2016; Peelle 2018). Because the dorsal attention network is extensively connected to auditory and visual cortex, it is also thought to contribute importantly to resource allocation during listening tasks (i.e., cognitive control). The network's hubs exhibit an anatomical layout that reflects its functional connectivity, with regions distributed centrally in frontal and parietal cortex in both hemispheres. This organization contrasts with the right-lateralized ventral attention network, which is proximal to auditory and frontal cortex regions that are critical to response inhibition. These differences appear to reflect the top-down communication between the dorsal network and sensory cortex for selective attention versus the bottom-up driven ventral attention orientation to salient acoustic stimuli (Sect. 10.7.2.1).

Selective attention appears to modulate early auditory processing of speech signals with activity changes in brainstem (Presacco et al. 2016) and auditory cortex (Fig. 10.3, red regions; Bonte et al. 2014), based on evidence of enhanced neural speech representations. Although selective attention for speech is poorer with increasing age at least for some tasks (Humes et al. 2006), these changes are challenging to interpret in the context of other potential age-related differences that may include hearing loss, poorer temporal and spectral precision (Babkoff and Fostick 2017), and cognitive declines (Wingfield et al. 2005). Because auditory and cognitive function are critical to the separation and selection of auditory information, age-related differences in either could be consequential to auditory selective attention.

10.7.2.3 Adaptive Control

As described in Sect. 10.3, the cingulo-opercular network comprises bilateral frontal opercula/AI and the dorsal ACC (Fig. 10.3, blue regions). Activity in this network is sensitive to increases in task demands and is proposed to signal for the recruitment of additional cognitive resources in support of successful task performance. The AI, particularly in the right hemisphere, may provide a link between the ventral attention orienting network (Sect. 10.7.2.1) and the cingulo-opercular network (Eckert et al. 2009). The ACC appears to function as a central a hub to facilitate the recruitment of other networks in support of accurate task performance. Indeed, in noisy and degraded listening conditions, robust activation can be observed throughout cingulo-opercular regions in frontal cortex. This cortical network is described as performing a domain-general *adaptive control* function to optimize task performance through ongoing neural and behavioral adjustments, and outcome monitoring (Vaden et al. 2013). Task difficulty and response errors increase cingulo-opercular activity, consistent with a performance monitoring function (Dosenbach et al. 2007). Numerous fMRI studies have shown that increased cingulo-opercular activity is associated with trial-level changes in performance that include faster response times and better task performance, indicative of its role in adjusting ongoing behavior. However, cingulo-opercular activity appears to have a diminished speech recognition benefit for older adults (Vaden et al. 2015).

Cingulo-opercular activity has been proposed to signal a redirection of cognitive resources (e.g., working memory, selective attention) to support speech recognition (Eckert et al. 2016). Evidence that cognitive resources are deployed for speech recognition comes from secondary task effects, where lowering the intelligibility of attended speech (primary task) worsens memory maintenance (secondary task; Rabbitt 1968). Cognitive abilities that include working memory span and processing speed also appear to support better speech recognition performance, especially for older adults (Wingfield et al. 2015). These largely behavioral observations indicate that cognitive resources can be directed to enhance speech understanding within the limits of an individual's cognitive abilities. Effortful listening has been proposed to relate to the intentional redirection of limited cognitive and perceptual resources for speech recognition in adverse conditions, which could result in listener fatigue to the extent that the benefit of resource allocation is outweighed by its cost (Eckert et al. 2016).

10.8 Neuroimaging Studies of the Impact of Aging on Motivation and Arousal

10.8.1 Value of Communication

The experience of listening effort has been proposed to reflect a mismatch between the cost of allocating mental resources for listening versus the reward from understanding speech (Eckert et al. 2016). In that context, effort may signal to a listener

that they should conserve resources instead of engaging additional resources in some contexts. To the extent that older adults have more limited resource capacities (Wingfield and Grossman 2006) or that older adults experience increased difficulty during the performance of noisy listening tasks (Reuter-Lorenz and Cappell 2008; Erb and Obleser 2013), the cost of listening effort may bias resource allocation to task conditions where additional resources can provide the greatest benefit. Factors such as motivation and reward are also hypothesized to shape the engagement of listening effort. Indeed, the cost-benefit tradeoff appears to change with age and sensorineural hearing loss and interacts with the benefit from hearing aid use (Eckert et al. 2017). A neuro-economic framework of communication value may contribute important new insights on age-related changes in resource allocation, cingulo-opercular activity, and pupillometric measures of listening effort (Eckert et al. 2016). Ultimately, communication value may provide behavioral and neural metrics for more targeted rehabilitation strategies for hearing aid users.

10.8.2 Sustained Attention, Vigilance, and Arousal

Aging has been associated with poorer adaptability to unexpected shifts in task demands (Ridderinkhof et al. 2002), which requires that individuals maintain vigilant attention for these changes (Dosenbach et al. 2006). As noted in Sect. 10.7.2.1, functional imaging studies have shown that sudden transitions, such as the onset of unexpected sounds or switching across blocks of conditions, elicit neural activity in auditory cortex (Huang et al. 2012) and the ventral attention network (Fox et al. 2005). Age-related changes within these systems may limit older adults' ability to sustain their attention and complete challenging speech tasks. In particular, older adults have been shown to exhibit marked interindividual variability in their auditory (Baum and Beauchamp 2014) and attention-related (Vaden et al. 2015) neural responses to speech.

Neurophysiological research has provided valuable insight into why older adults may experience declines in vigilant attention that impair speech perception. Noradrenergic activity, driven by the firing of neurons in the locus coeruleus (LC) brainstem nucleus, alters the engagement of sensory- and attention-related cortex (Aston-Jones and Cohen 2005) and thus vigilant attention (Hermans et al. 2011). Age-related declines in the number of LC neurons (Manaye et al. 1995) are thought to broadly reduce task engagement and arousal among older adults (Jennings et al. 1988; Levenson et al. 1991). Kuchinsky et al. (2016) investigated this link in a speech recognition fMRI study that also collected pupillometry, a marker of LC activity (Joshi et al. 2016). Older adults who exerted greater effort during the task (larger task-evoked pupil responses) scored higher on a standardized measure of vigilance and engaged more extensive portions of auditory cortex in response to unexpected task transitions. Together these findings suggest that maintaining vigilant attention to speech is associated with greater effort among older adults. The

extent to which sustained effortful listening over long periods of time leads to daily-life fatigue for older adults and individuals with hearing loss is an important outstanding question (Alhanbali et al. 2017).

10.9 Clinical Implications and Future Directions

This chapter began by noting that a common complaint among older adults is the feeling of exhaustion when listening to speech in adverse conditions, such as in background noise. As was reviewed, neuroimaging can help clarify whether individuals experience difficulty in certain listening conditions and which conditions might see performance improvements, beyond what can be learned from recognition accuracy. Most of the conclusions are based on the results of data analyzed across a group or groups of participants. However clinical decisions, diagnoses, and interventions need to be made accurately for each individual patient. What, then, is the role of neuroimaging for improving our ability to assess and remediate effortful listening in the clinic? Given the expense, exclusionary criteria, and analytical complexity of most neuroimaging methods, it is unlikely that one would recommend that everyone complete an fMRI task to measure listening effort. On the other hand, subjective measures of effort, relatively trivial to collect, are subject to a number of biases that can limit their interpretability. Individuals may have poor insight into their own impairments and some populations may incorrectly judge their level of effort.

Thus, the role of neuroimaging may be (1) to improve the assessment of effort by validating other more clinically feasible measures of effortful listening and/or (2) to facilitate the development and evaluation of novel clinical interventions, such as a new training program or hearing aid algorithm, in a laboratory setting. For example, some studies have sought to link behavioral and physiological measures (e.g., pupillometry) to the neural systems that underlie effortful listening (Zekveld et al. 2014). In doing so, insight can be gained into the extent to which the mechanisms engaged during effortful listening can be tracked using less costly, more accessible techniques.

10.9.1 Targeted Assessments

At present, brain imaging techniques are too expensive and time-consuming to use as a clinical tool for studying auditory function in individual patients who are otherwise healthy. Furthermore, metal implants and conditions such as back pain can preclude safe and comfortable MRI data collection for many older adults. Finally, there are no benchmarks for reliable characterization of an individual's brain activity based on fMRI. Unlike raw structural brain images that can be read by a radiologist without image processing, fMRI requires a suitable protocol to present stimuli

consistently to participants, extensive signal preprocessing of the image data, and often a knowledgeable signal analyst to determine whether physiological, motion, or other confounds contaminated the measurements.

Alternative physiological measures may avoid some of the cost, artifact, and safety issues inherent in other measures. Fluctuations in the pupil dilation response to auditory presentations have been shown to track listening effort in younger and older adults with normal to impaired hearing. In general, the pupillary response tends to be larger and slower to peak in more challenging listening conditions (for a review see Zekveld et al. 2018). Echoing the nonlinear relationship between task demands and effort observed with neuroimaging (Fig. 10.2), the pupil response also tends to be maximal at moderate levels of task difficulty and fall off as the task becomes easier or impossibly hard (Ohlenforst et al. 2017). Pupillometry has been described as a "reporter variable" of the functioning of the locus coeruleus-norepinephrine (LC-NE) system that modulates states of attention (Gilzenrat et al. 2010) and has connections with the cingulo-opercular network. Indeed, a number of studies have sought to validate pupillometry as an objective indicator of mental effort by linking it to the sensory and attentional neural systems that are engaged in effortful listening. Zekveld et al. (2014), for example, showed that increased pupil dilation was associated with greater activity in bilateral superior temporal gyri and the left AI. However, given that the LC-NE is a neuromodulatory system with widespread projections throughout cortex, it is unclear whether the pupil response indexes activity in a particular brain network or rather is a broad summary measure of ongoing activity across the brain in challenging conditions (Winn et al. 2018). Neuroimaging work must further validate the extent to which the pupillary response, or specific components of it (e.g., peak amplitude, latency), track the neural systems engaged during effortful listening. In this way, pupillometry may provide insight into the mechanisms that contribute to complaints of speech recognition difficulties, and thus guide the development of remediations that target those underlying issues.

Although pupillometry has been shown to consistently reveal differences in listening effort at the group level, its utility at the individual level, which is paramount for clinical assessments, is not well established (for a discussion see Winn et al. 2018). Thus, in their current state, physiological measures may be more useful for examining changes in effort with aging, hearing loss, and with intervention at the group level in a laboratory. However, the rapid advancement of sensor technology and its integration into smart devices suggests that it will become increasingly easy to unobtrusively collect physiological data on a large scale. This would allow researchers to develop norms for evaluating effort within an individual in a clinical setting.

Due to the widespread clinical applications of structural imaging, MRI technology continues to improve and provide quieter, faster, and higher-resolution data. Functional MRI holds promise for characterizing cortical function in relation to declines in audition and speech recognition based on biomarkers at successive stages in the central auditory nervous system, although this requires protocol standardization and multidisciplinary expertise. Such endeavors have led to fMRI-based

language dominance tests for presurgical clinical assessments of patients with severe epilepsy, which is the main clinical application of fMRI.

At present, functional neuroimaging provides validation for increasingly mechanistic models of age-related changes in audition, attention, and listening effort. As described in Sect. 10.3 (Figs. 10.1 and 10.2), behavioral measures can conceal changes in effort and attention with enormous consequences for the engagement of extensive brain networks. This suggests the importance of reliable estimation and interpretation of functional network engagement during speech recognition. While this research can significantly improve our understanding of the aging brain and how it supports speech recognition in difficult conditions, assessing individual patients with fMRI is not currently feasible.

Structural neuroimaging techniques such as diffusion imaging and MR spectroscopy may provide important clinical information to assess potential age-related declines within the central auditory nervous system. Diffusion tensor imaging data can provide information about the structure of large-scale white matter tracts and cortex. MR spectroscopy data may be sensitive to the concentration of neurotransmitters in specific brain regions, such as reduced GABA in the central auditory pathway (Caspary et al. 1995). While each method requires extensive data processing and is susceptible to artifacts (much like fMRI), they can provide important details about the structure and neurochemistry of an individual's brain.

10.9.2 Targeted Interventions

Identifying the mechanisms that underlie age-related changes in effortful listening means that interventions can be tuned to optimally target them. Many training-based interventions have focused on developing tasks that engage auditory perceptual processes that could be more susceptible to age-related changes (e.g., Caspary et al. 1995). Given that age-related changes occur at multiple levels of speech processing, training strategies to address both auditory and cognitive function may more comprehensively remediate the range of listening difficulties that older adults experience. In particular, interventions that train executive functions within auditory tasks have been hypothesized to yield better outcomes for speech understanding in noise compared to auditory-only training by targeting more of the functions that support speech recognition in noise (Ferguson and Henshaw 2015).

Neuroimaging may also prove useful for identifying candidate training tasks and conditions that are most likely to improve speech recognition. Previous auditory and cognitive training protocols have generally aimed to train a broad array of sensory and executive functions over many trials and sessions and yet had limited benefits for cognitive function in older adults with hearing loss (for a review see Lawrence et al. 2018). However, the likelihood that trained skills will transfer to new conditions often depends on the similarity of cognitive and neural systems engaged by each (Hussey and Novick 2012). Thus, neuroimaging research may improve the

development of interventions by revealing the extent to which a given training task engages systems that are affected by aging and hearing loss or leverages unaffected systems to compensate for changes in performance.

Targeted neural interventions such as brain stimulation are currently in development for treating neurological disorders, which could eventually generalize to communication disorders that include listening difficulties. For example, transcutaneous vagal nerve stimulation (tVNS) is a noninvasive approach by which a low-voltage electrical current is applied to peripheral afferents of the vagus nerve, such as the auricular branch of the vagus in the outer ear canal, to stimulate brainstem regions including the LC. While the effectiveness of tVNS for inducing auditory neuroplasticity has been examined primarily in animal models or in humans with implanted neurostimulation systems, there is some evidence for tVNS's effectiveness in treating tinnitus in humans noninvasively (Lehtimäki et al. 2013). Traditional neuroimaging tools may help in providing cortical or network-level targets for such an approach.

10.10 Summary

Neuroimaging research has provided important insights into the mechanisms that underlie effortful listening and how they change with aging and hearing loss. The engagement of sensory, linguistic, and executive functions contributes to successful speech recognition. Older adults have been observed to upregulate more extensive, diffuse regions of these neural systems than do younger, normal-hearing individuals. This additional activity may provide a compensatory benefit: decrements in speech understanding may be mitigated by increasing effort. However, as listening becomes impossibly difficult, increasing activity within additional cortical regions may be insufficient to compensate. Drops in performance may be observed as individuals experience diminishing returns from effort and give up. Understanding how individuals balance effort and speech recognition performance may be particularly critical for developing improved assessments and effective remediation for the problems faced by older adult listeners.

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Chapter 11
Functional Consequences of Impaired Hearing in Older Adults and Implications for Intervention

Larry E. Humes, M. Kathleen Pichora-Fuller, and Louise Hickson

Abstract This chapter considers the consequences of aging on communication and the ability to age well in terms of participation in everyday life. Interventions designed to reduce the negative effects of age-related hearing impairment on communication and participation are also described. These interventions span technological, behavioral, and environmental approaches. Based on correlations between measured speech-recognition or self-report surveys of communication and pure-tone thresholds, it is estimated that the inaudibility of speech may fully explain the speech-communication difficulties experienced by about half of older adults. For these individuals, hearing aids compensating for this inaudibility may be sufficient to remediate the speech-communication problems they experience. For the remainder of older adults, however, their problems are more complex and may be attributable to auditory neural, central-auditory, or cognitive deficits, with or without accompanying pure-tone hearing loss. Furthermore, psychological and social adjustment to hearing loss may require nontechnological solutions. Such adjustment may be complicated by the interface between hearing loss and other age-related comorbidities that affect optimal participation and aging well. Devices such as hearing aids in and of themselves are likely to be insufficient to remediate the difficulties experienced by these older adults. Complementary or supplementary interventions are needed to fully address their functional deficits and to reduce the participation restrictions or activity limitations experienced by older adults with hearing loss and speech-communication difficulties.

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11.1 Introduction

Age-related hearing impairment (ARHI; a full list of abbreviations used in this chapter is provided in Table 11.1), is manifest in millions of individuals throughout the world and it is associated with many other age-related health issues (Deal et al., Chap. 8). The World Health Organization (WHO 2013) reported that roughly one-third of persons age 65 years and older, or a global estimate of 164.5 million people, are affected by disabling hearing impairment. A 2015 report on the Global Burden of Disease estimated that hearing loss and vision loss, respectively, were the second and third most common impairments world-wide (Vos et al. 2016). Knowledge of

Table 11.1 Abbreviations used in this chapter

4fPTA	four-frequency (0.5, 1, 2, and 4 kHz) pure-tone average
AB	audiology-based
ARHI	age-related hearing impairment
BTE	behind-the-ear
CD	consumer-decides
CLSA	Canadian Longitudinal Study of Aging
COSI	Client-Oriented Scale of Improvement
CST	Connected Speech Test
CSTben	differences between aided and unaided scores on the CST
GPS	Goal Partnership Strategy
HHIE	Hearing Handicap Inventory for the Elderly
HHIEben	difference between aided and unaided scores on the Hearing Handicap Inventory for the Elderly
HHIE-S	Hearing Handicap Inventory for the Elderly–Screening version
HI	hearing impairment
HII-SOP	Hearing Impairment Impact–Significant Other Profile
ICF	International Classification of Functioning
P	placebo
PHAB	Profile of Hearing Aid Benefit
PHAB_avds	subscale score from the Aversiveness and Distortion PHAB scales
PHAB_Glob,	global subscale score from the PHAB
PTA	pure-tone average
SOS-HEAR	Significant Other Scale for Hearing

the biology of ARHI and how the auditory system changes with age from the cochlea to the cortex has advanced greatly (Someya, Chap. 2; Ohlemiller, Chap. 3; Syka, Chap. 4; Recanzone, Chap. 5), as has knowledge of the physiological (Harris, Chap. 6; Kuchinsky and Vaden, Chap. 10), perceptual, and cognitive (Gallun and Best, Chap. 7; Gordon-Salant et al., Chap. 9) characterizations of how older adults perform on many tasks that may be relevant to listening in everyday life.

Knowledge about the biological, physiological, perceptual, and cognitive aspects of auditory aging helps us to understand the (dis)abilities of older listeners. However, to understand fully the effects of auditory aging on functioning in everyday life, knowledge of the (dis)abilities of older listeners must be understood more ecologically by considering individuals in the context of their environments. The ultimate goal of aging research is to optimize aging so that people live better and longer. A general principle of aging well is that the person–environment fit should be optimized (Wahl et al. 2012). Insofar as hearing health is a key component of healthy aging, it is reasonable that the ultimate goal of intervention for ARHI is to enable older adults to function optimally as listeners so that they can achieve their goals for participation in everyday life as fully as possible, thereby increasing their opportunities to live better and longer. Interventions to optimize functioning in everyday life must strive to improve the fit between older listeners and their environments.

11.2 The World Health Organization International Classification of Functioning, Disability, and Health

The WHO International Classification of Functioning (ICF) (WHO 2001) provides a framework for considering the biopsychosocial–environmental effects of health conditions on the lives of people. The holistic nature of the ICF is particularly useful when discussing interventions for ARHI (Kiessling et al. 2003). Therefore, it will be used to organize the information provided in this chapter. In Sect. 11.2, the issues of ARHI will be mapped to the domains of the ICF. In Sect. 11.3, interventions to address those issues will be discussed.

Figure 11.1 shows the domains of the ICF and the effects of changes in hearing associated with aging in each domain for an example individual with ARHI (Grenness et al. 2016). Impairments are negative changes of body structure and function that are associated with ARHI; for example, loss of cochlear hair cells in the auditory periphery (Ohlemiller, Chap. 3) is a change at the level of body structure and decreased audibility of sound as measured by audiometry is a loss of function. Activity limitations are difficulties that arise in the execution of a task, with typical examples being problems understanding speech in the presence of background noise or difficulties hearing the television or radio. Participation restrictions and activity limitations are the problems that people experience in their everyday social situations due to ARHI. Withdrawing from social situations is a commonly

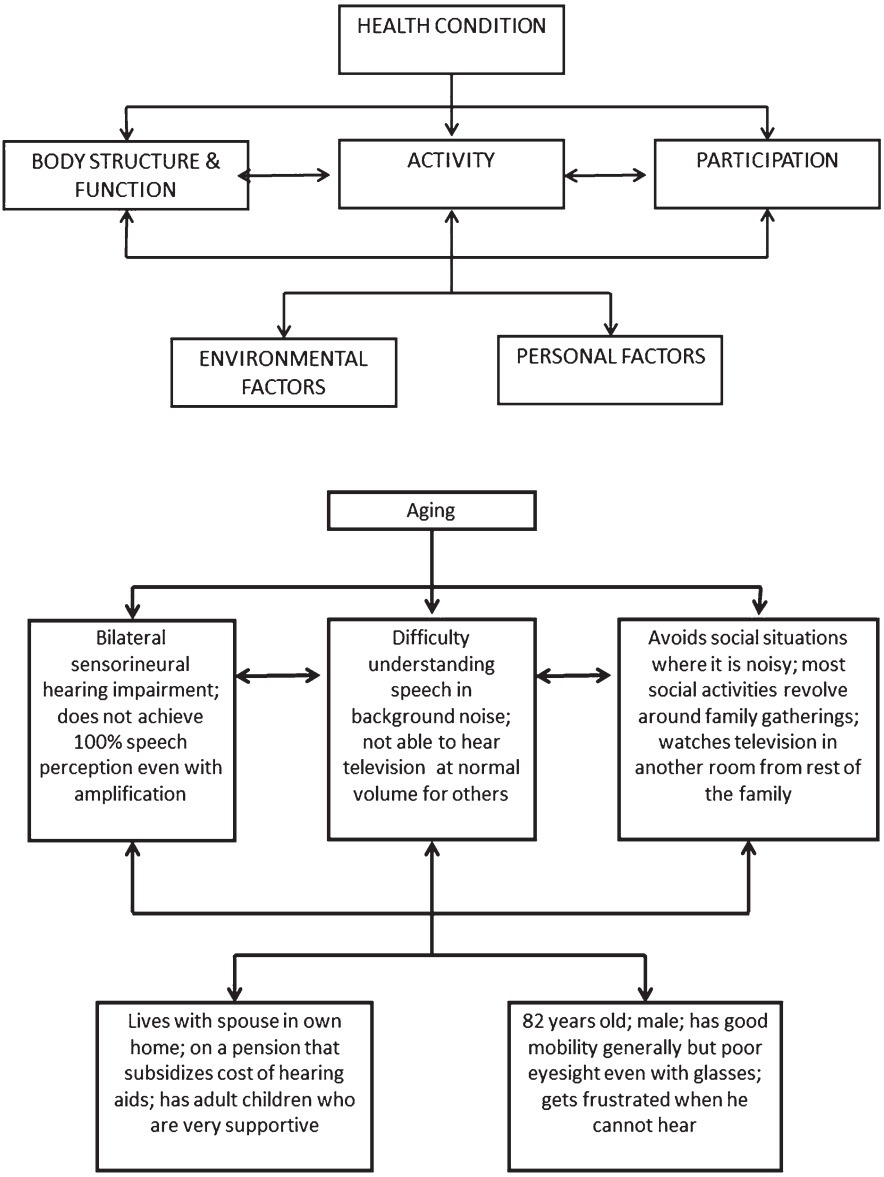

Fig. 11.1 This schematic shows the domains of the WHO ICF (top) and the effects of the changes in hearing associated with aging in each domain for an example individual (bottom). (Based on Grenness et al. 2016)

reported restriction of older adults with ARHI. In the ICF, the word "disability" is used to encompass impairments, activity limitations, and participation restrictions.

Although there are correlations between the various domains of disability, such that the greater the hearing impairment, the more activity limitations and participation restrictions an older adult is likely to experience, correlations between these domains are only moderate at best (Matthews et al. 1990; Kramer et al. 1996). Figure 11.2 shows the distribution of a measure of hearing impairment based on an average of pure-tone audiometric thresholds (pure-tone average [PTA] of 1, 2, 3, and 4 kHz in the better ear) for responses by over 30,000 people in the Canadian Longitudinal Study of Aging (CLSA) who reported their hearing, using aids if applicable, to be excellent, very good, good, fair or poor. The median PTA increased as self-reported hearing became worse; however, every self-reported category of hearing was possible even for those whose PTA was in the normal range (<25 dB HL). With age, the prevalence of both behaviorally measured hearing impairment defined by PTA and self-reported hearing problems increase; for middle-aged adults, estimates of the prevalence of hearing impairment are greater when based on self-report compared to behavioral measures, but after 65 years of age the pattern

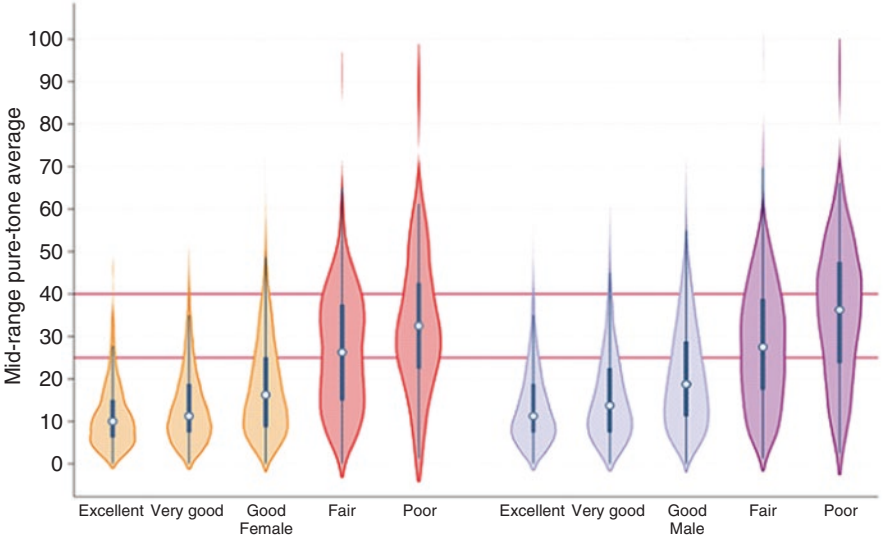

Fig. 11.2 Violin plots for the better ear pure-tone average (BPTA) of audiometric thresholds at 1, 2, 3, and 4 kHz for each category of self-reported hearing ability for more than 30,000 men and women who participated in the Canadian Longitudinal Study of Aging. The shape of the violin area shows the distribution of the BPTA data; circle indicates group-specific median, with the surrounding vertical bars indicating the percentiles (thick line: interquartile range (25th and 75th percentiles); thin line: 95% confidence interval). Fair and poor self-reported hearing (red for women and purple for men) are taken to indicate self-reported sensory difficulties as experienced in everyday life. Horizontal reference lines indicate the thresholds for mild (<25 dB HL) and moderate (25–40 dB HL) hearing loss (see also Hämäläinen et al. 2019)

reverses, with the estimated prevalence being less when based on self-report compared to behavioral measures (Bainbridge and Wallhagen 2014).

Why would all people with normal audiograms not report their hearing to be at least very good or people with moderate loss not report their hearing to be poor? Answers to such questions may be found in the contextual factors (personal and environmental) in the ICF framework. Contextual factors help to explain individual differences between measures of impairment, such as audiometric thresholds, and the individual's appraisal of hearing function based on experiences of activity limitations and participation restrictions in everyday life. Controlling for audiometric thresholds, examples of personal factors that were associated with worse self-reported hearing by participants in the CLSA were older age, being male, having poorer self-reported vision, and having a greater number of comorbid health conditions. Examples of relevant environmental factors were the number of people with whom the person interacted within his or her social network and how much the person participated independently in activities outside the home, with better self-reported hearing being associated with greater social interaction and participation (Hämäläinen et al. 2019). Interventions for ARHI that will help older adults to age well may involve only one of the ICF domains, but it is more likely that the most effective interventions will involve all the ICF domains.

11.2.1 Hearing Impairment

11.2.1.1 Pure-Tone Audiometric Profiles

A recently proposed WHO definition of disabling hearing impairment in adults is a better-ear four-frequency (0.5, 1, 2, and 4 kHz) pure-tone average (4fPTA) of greater than 35 dB HL, corresponding to a WHO hearing-impairment grade of "2" or a "moderate" hearing impairment (Stevens et al. 2013). This proposed definition of "moderate" hearing impairment (HI), considered to be the onset of disabling HI, differs slightly from the WHO definition that has prevailed since 1991 (WHO 1991). Whereas the proposed definition of "moderate" impairment is based on a better-ear 4fPTA from 35 to 50 dB HL, the prior definition spanned better-ear 4fPTA from 40 to 60 dB HL. Figure 11.3 compares the two WHO HI grade systems and the adjectives reflecting the impairment severity assigned to each. To avoid confusion, we refer to the proposed WHO HI grade system as "WHO-new HI" and the prevailing system as "WHO HI."

11.2.1.2 Speech Understanding

Audiometric thresholds can be used to estimate the audibility of speech information that serves speech understanding. In both panels of Fig. 11.4, the dashed line depicts the long-term-average spectrum of speech at a conversational level (Pavlovic 1989).

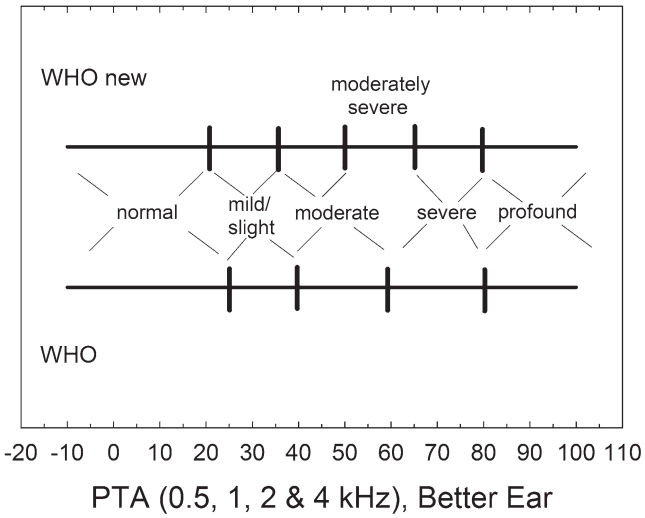

Fig. 11.3 Comparison of the 1991 WHO HI grade system (bottom) to the proposed WHO-new HI grade system (top). The general pattern from original to proposed WHO grade systems is to move severity categories of "mild" and "moderate" to lower PTA values and "severe" to a higher PTA value to make room for a new intermediate category, "moderately severe." See text for a description of other changes between the 1991 and 2013 versions of the WHO HI grade system. HI, hearing impairment; PTA, pure-tone average; WHO, World Health Organization

The speech energy at and above 1 kHz contributes about 70% of the information needed for speech intelligibility. Clearly, much of the important speech information is rendered inaudible by the hearing impairment of the typical 60-, 70-, and 80-year-old men and women (Fig. 11.4).

As noted, the emphasis in the ICF (WHO 2001) is on the functioning of the person and on whether an impairment limits everyday activities and restricts the person's participation in society. Within this framework, pure-tone audiometry may be a reasonable metric for *impairment* to the bodily structures or functions associated with aging, although even that might be debated, but it may not be reflective of the associated effects on a person's *activities* or *participation* in society. A link between pure-tone-based indices of impairment and functional deficits in communication is implied by the WHO-new HI grade system (Stevens et al. 2013). Insofar as participation in society depends on communication function, which usually entails understanding speech, a useful first step would be to determine the extent to which there is correspondence between pure-tone audiometry and performance on tests of speech understanding.

Humes (2019a, b) evaluated the validity of the WHO and WHO-new HI grade systems by determining the correspondence between pure-tone audiometry and speech test results. His studies examined data from several large unscreened samples of older adults that included measures such as speech-recognition performance for tests using monosyllabic words presented in quiet or noise and self-report

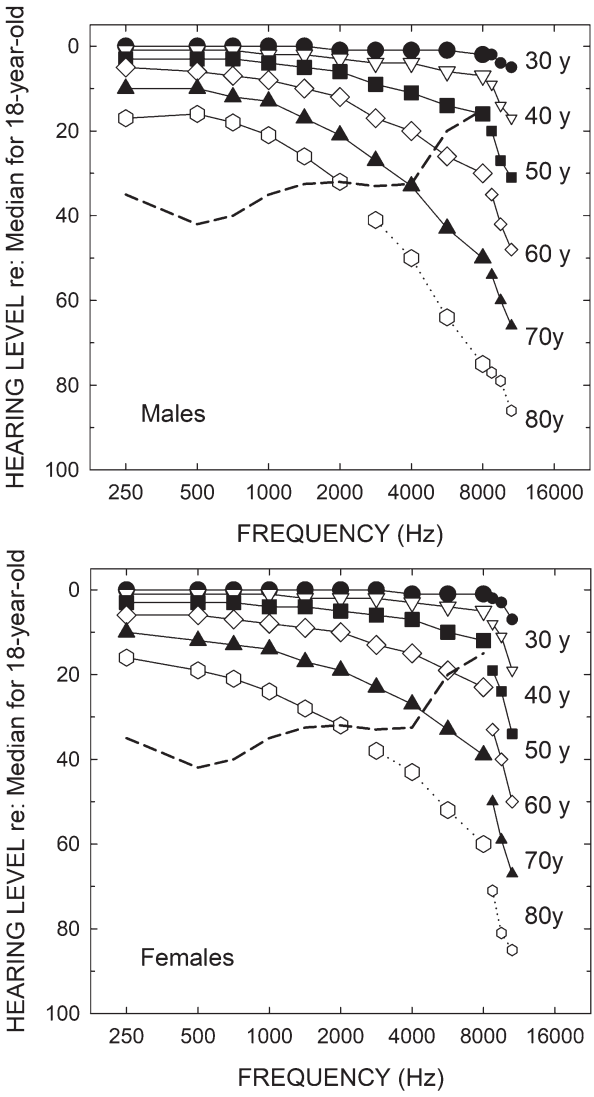

Fig. 11.4 Progression of age-related hearing impairment by decade for males (top) and females (bottom). Median values from ISO-7029 (2017) are shown by the symbols. Dotted lines connect best estimates from the ISO standard, but the supporting data are limited and the estimates considered tentative. The dashed line in each panel represents the long-term-average speech spectrum for conversational speech on these same coordinates (Pavlovic 1989)

surveys of hearing difficulty. Figure 11.5 provides results that are representative of the findings (Humes 2019a). Data pooled from a large population sample in Australia (Golding et al. 2004) and a large clinical sample in the United States (Wilson 2011) were analyzed. Data were available from more than 5600 adults, who were mostly over 50 years of age, with each study contributing roughly equal shares to the merged dataset. Figure 11.5 depicts the means and standard deviations for the recognition of monosyllabic words presented at moderate-to-high presentation levels in quiet under headphones. Scores are shown separately for right and left ears and the WHO-new HI grade was calculated separately for each ear. Overall, for

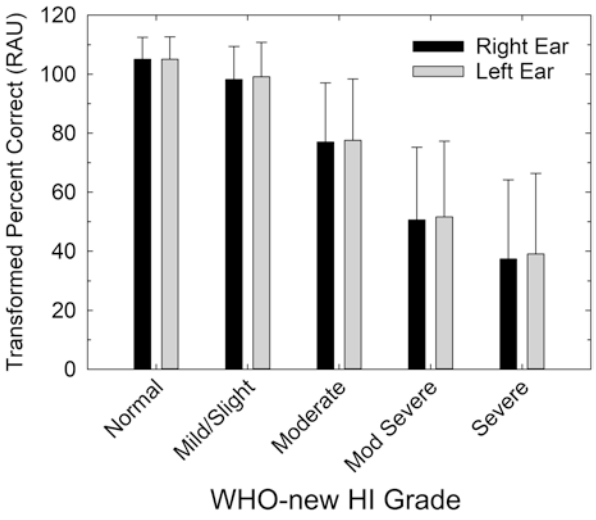

Fig. 11.5 Means and standard deviations for the pooled data from Golding et al. (2004) and Wilson (2011) showing average word-recognition scores (in rationalized arcsine units [RAU]) obtained under headphones in quiet plotted as a function of WHO-new HI grade for the corresponding ear

these measures of speech recognition performance in quiet, as WHO-new HI grade increases, speech-recognition performance decreases.

The pattern of findings for the data shown in Fig. 11.5 are representative of the more detailed and thorough analyses presented in Humes (2019a) for speech recognition in quiet and in noise. These findings support the validity of the pure-tone-based definition of hearing impairment grade established by WHO, at least for the "average" older adult with hearing impairment severity defined according to the WHO-new HI grade.

Although progression up the scale in the pure-tone-based severity of hearing impairment in average older adults yields successive declines in speech-recognition scores in quiet (Fig. 11.5) and in noise (Humes 2019a, b), the question remains as to the grade or category at which disability begins. As noted, WHO (2013) defines disabling hearing impairment as beginning at a WHO-new HI grade of 2 or "moderate" with the 4fPTA exceeding 35 dB HL. Importantly, given medium-to-large effect sizes with every increment along the WHO-new HI grade system (Humes 2019a, b), including from "normal" to "mild/slight," it could be argued that disabling HI begins with the grade of 1 or "mild/slight" HI. Further large-scale studies of older adults are needed to better establish the correspondence between the severity of ARHI and its effects on everyday activities and participation in society beyond the direct effects on hearing thresholds and relatively artificial measures of speech communication. Clinically measured speech-recognition under headphones in quiet, for example, is not necessarily representative of the "typical" everyday communication demands experienced by older adults. Even when large-scale studies

have included standardized measures of speech-recognition in noise, the stimuli and listening conditions are often constrained and have questionable ecological validity. Moreover, the focus of prior research has been placed on the effect of HI on speech communication, but this focus neglects other relevant aspects of everyday listening experiences, such as the perception of music or environmental sounds. More research is needed to investigate whether the onset of "disabling" hearing loss begins at the "mild" or "moderate" WHO-new HI grade and if classifications based on pure-tone thresholds need to be augmented by other criteria. Such information could help guide the decisions of policymakers and third-party payers regarding the need for and funding of interventions.

11.2.2 Activity Limitations and Participation Restrictions

HI in older adults is often associated with far-reaching negative effects on activity and participation, even when pure-tone thresholds may suggest otherwise (Fig. 11.2). Examining the ICF codes related to functioning and disability and the core set of activity limitations and participation restrictions that are relevant to people with ARHI (Granberg et al. 2014a, b), it is apparent that their difficulties in everyday life are likely to involve listening, having conversations, creating and maintaining family relationships, handling stress, and engaging in community life.

11.2.2.1 Interview Data from Older Adults and Their Communication Partners

Common approaches in research and clinical practice to evaluate activity limitations and participation restrictions are (1) to interview older adults, their communication partners, or both; and (2) to ask them to complete questionnaires. Barker et al. (2017) provide a qualitative meta-synthesis of 12 interview studies of older adults and communication partners in which several activity limitations and participation restrictions were reported to be experienced. For example, HI leads to communication breakdowns and this can limit social and leisure activities and participation for both individuals with HI and their significant others. Other reported effects were frustration, anxiety, and depression. A systematic review of 26 clinical or epidemiological studies also found that the communication partners of those with impaired hearing experienced restricted social life and poorer quality of life and relationship satisfaction than the partners of those with normal hearing (Kamil and Lin 2015). The adverse effects of HI on communication partners and family members is referred to by the WHO as third-party disability (Scarinci et al. 2008). Third-party disability is described further in Sect. 11.2.3.2.

11.2.2.2 Questionnaire Data from Older Adults and Their Communication Partners

Numerous questionnaire measures have been developed to survey older adults about their activity limitations and participation restrictions, with some specifically targeting the ARHI population. The most common such measure is the 25-item Hearing Handicap Inventory for the Elderly (HHIE; Ventry and Weinstein 1982) and its shorter screening version, the 10-item Hearing Handicap Inventory for the Elderly–Screening version (HHIE-S; Ventry and Weinstein 1983). Questions relate to activity (e.g., *Do you have difficulty hearing when someone speaks in a whisper?*), participation (e.g., *Does a hearing problem cause you to avoid groups of people?*), and to the broader quality of life effects of HI (e.g., *Does any problem or difficulty with your hearing upset you at all?*). Response options are yes (4 points), sometimes (2 points), and no (0 points), with higher total scores being indicative of greater disability.

Questionnaires for people with HI have been used for decades, but these have seldom been used to assess the experiences of communication partners. Two questionnaires about third-party disability associated with HI are the 27-item Significant Other Scale for Hearing (SOS-HEAR; Scarinci et al. 2009) and the 20-item Hearing Impairment Impact–Significant Other Profile (HII-SOP; Preminger and Meeks 2012). An example item from the SOS-HEAR is *Because of my partner's hearing difficulties I have to repeat myself often*; the questionnaire has a 5-point response scale from no problem (0 points) to a complete problem (4 points). An example from the HII-SOP is *Because of your significant other's hearing loss, do you talk less often than you used to?*; response options are the same as for the HHIE (yes 4 points, sometimes 2 points, and no 0 points). For both measures, higher total scores are indicative of greater disability.

11.2.2.3 Associations of Hearing Impairment with Self-Reported Disability

Figure 11.6 depicts the means and standard deviations for the HHIE-S data pooled from the studies of Golding et al. (2004) and Wilson (2011) plotted versus the better-ear WHO-new HI grade. In general, the data in Fig. 11.6 indicate that, as the severity of HI increases, regardless of age, the self-reported activity limitations and participation restrictions of older adults also increase. These results further validate the WHO-new HI grade system and illustrate the linkages between the domains of impairment, activity limitations, and participation restrictions, at least based on averages.

Although the data for the HHIE-S in Fig. 11.6 suggest a neat relationship between the severity of HI as captured by pure-tone thresholds and the resulting effects on activity limitations and participation restrictions as measured by the HHIE-S on a group basis, the scatterplot of these same data in Fig. 11.7 indicates that this association is not so tidy. For a given level of sensory impairment measured by pure-tone

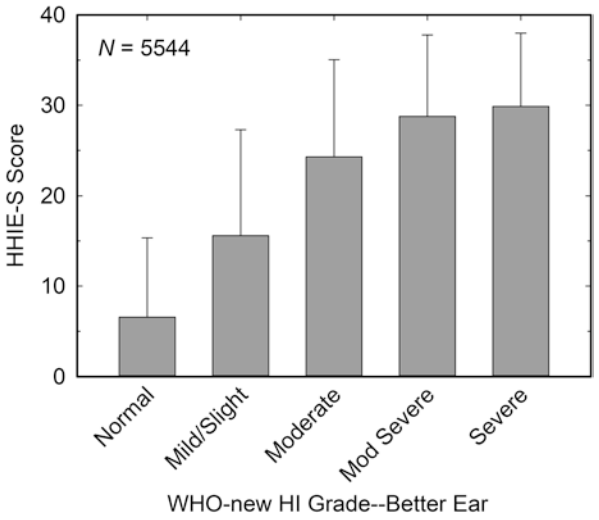

Fig. 11.6 Means and standard deviations for the pooled data from Golding et al. (2004) and Wilson (2011) showing average HHIE-S scores as a function of WHO-new HI grade for the better ear. HHIE-S, Hearing Handicap Inventory for the Elderly–Screener

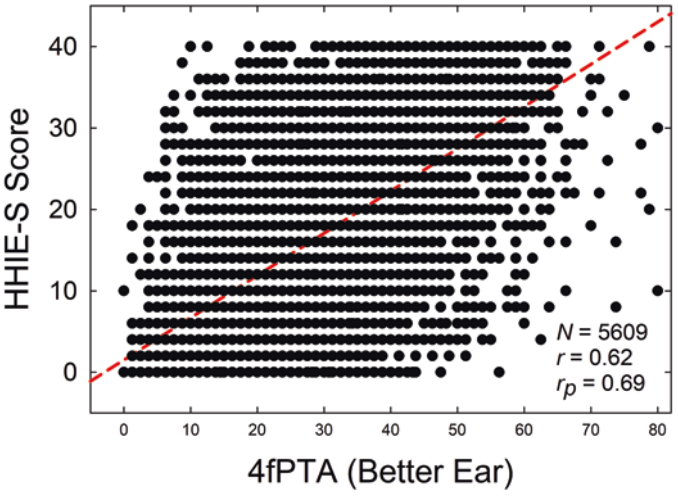

Fig. 11.7 The same dataset used in Fig. 11.6 but presented as individual data here. The correlations at the lower right represent the Pearson-*r* value (0.62) and the partial correlation when controlling for age (0.69). 4fPTA, pure-tone average for 0.5, 1, 2, and 4 kHz. The red line is the best-fitting line derived using linear regression

audiometry, there can be a wide range of effects on the whole person. Partialling out the effects of age on 4fPTA ($r = 0.40$) yields a slightly higher partial correlation between 4fPTA and HHIE-s of $r_p = 0.69$ compared to the correlation of $r = 0.62$ without partialling out age. Due to the large N, the correlation between age and HHIE-S was significant ($p < 0.01$) but near zero ($r = -0.05$), suggesting the direct effect of age on HHIE-S in this pooled sample was not meaningful. Using either the 0.62 or the 0.69 value for the correlation between 4fPTA and HHIE-S, it appears that the impairment measured using pure-tone audiometry captures about 35–50% of the individual variation in activity limitation and participation restriction measured by the HHIE-S. However, this must be evaluated against the systematic variance for the HHIE-S, which based on a test–retest correlation of $r = 0.85$ (Ventry and Weinstein 1982; Tomioka et al. 2013), would be about 72%. Thus, roughly half (35%/72%) to two-thirds (50%/72%) of the reliable individual variations (or "systematic variance") in HHIE-S scores in Fig. 11.7 may be explained by 4fPTA. Clearly, other factors beyond the pure-tone-based impairment must contribute. Such factors may include age-related changes in peripheral and central-auditory neural structure and function not captured by pure-tone audiometric thresholds, as well as nonauditory factors, including age-related changes in cognition and a variety of contextual factors (Pichora-Fuller et al. 2017).

11.2.3 Contextual Factors

There are numerous personal and environmental factors that influence how individuals with similar audiograms function in everyday life. In this section, some of the factors that are most relevant for adults with ARHI are discussed. Such factors may also influence the uptake and outcomes of interventions as discussed in Sect. 11.3.

11.2.3.1 Personal Factors

11.2.3.1.1 Suprathreshold Deficits in Auditory Processing

As noted, the WHO HI grade systems classify the severity of damage to the bodily structures and functions of hearing on the basis of better-ear 4fPTA. This audiometric measure can, at best, account for half to two-thirds of the measured speech-communication problems in older adults (Sect. 11.2.2.3). Beyond the audiogram, there is strong evidence that a variety of declines in auditory temporal processing, thought to be critical to speech understanding, especially in noise, are also impaired in many older adults (for a review see Humes et al. 2012). Listening in everyday life can also be affected by age-related changes in cognitive processing that interact with auditory aging (Pichora-Fuller et al. 2017; Pichora-Fuller 2020). Two older adults of the same age who have the same audiogram may differ in their

auditory-cognitive processing of information (Gallun and Best, Chap. 7; Gordon-Salant et al., Chap. 9; Kuchinsky and Vaden, Chap. 10). Thus, some of the residual variability not explained by the 4fPTA (Fig. 11.7) is likely explained by age-related changes in the higher-level processing of auditory signals and how listening interacts with other tasks that often co-occur in the context of everyday situations.

11.2.3.1.2 Comorbidities

Of many personal contextual factors, one of the most relevant to older adults with ARHI may be the presence of comorbid health conditions. Multimorbidity is one of the greatest challenges in providing health care to address the functional needs of older adults (American Geriatrics Society 2012), including those with HI (Abrams 2017). A survey of almost 2000 adults (18–70 years old) found that at least one chronic health condition (other than HI) was reported by 79% of those who self-reported hearing loss compared to 68% of those who reported having good hearing (Stam et al. 2014). In one geriatric audiology clinic, 84% of those seen for hearing aid evaluations had more than one comorbidity and the number of comorbidities increased with age (Dupuis et al. 2019). Comorbidities that are associated with HI include cognitive impairment, visual impairment, balance/mobility restrictions, mental health problems (e.g., depression, anxiety), diabetes, cardiovascular disease, stroke, arthritis, and cancer (Besser et al. 2018). Some comorbidities (e.g., diabetes) increase risk of hearing loss and the risk of other comorbid conditions that interact with hearing loss (e.g., vision loss). Conversely, hearing loss increases the risk of some comorbidities (e.g., dementia, falls). The comorbidities that may be the most directly relevant to older adults with ARHI are declines in cognition, vision, and balance/mobility because they combine to affect communication and participation (Wettstein et al. 2018). Other comorbidities (e.g., declines in dexterity related to conditions such as arthritis) may be relevant because they affect the successful uptake and use of devices (Singh 2010). The connections between ARHI and comorbidities are reviewed in more detail in Chap. 8 by Deal et al.

11.2.3.2 Environmental Factors

In terms of environmental contextual factors, an older adult's experiences of HI may be highly influenced by physical or social environmental factors in their living situation at home and as members of the community. The features of the physical environment can support or compromise communication and participation depending on acoustical factors (e.g., the amount of background noise and reverberation), lighting, or even the arrangement of furniture (e.g., seating so that conversationalists can see each other's faces). Personal or public technologies to support communication may help to optimize functioning in what would otherwise be challenging physical spaces (see Sect. 11.3). The social environment includes the nature of support received from significant others and familiar communication partners and the

behaviors of strangers with whom people might interact in the community (e.g., bus drivers, bank tellers, healthcare providers).

The effects of the physical-spatial-technical and social aspects of the environment on older adults have been integrated in an ecological model of aging well (Wahl et al. 2012) that is consistent with the WHO ICF. Environmental supports may be critical to successful social participation; without environmental supports, older adults may become socially isolated, and social isolation may, in turn, compromise mental and physical health (Pichora-Fuller et al. 2015). The environments of older adults include private, shared, and public places. Although older adults would prefer to "age in place," they may need to receive increasing informal or formal support to continue to live in their own home, and eventually they may engage in day programs or move into a residential care facility where more support can be provided. As hearing loss and other comorbidities increase with age, the ability of older adults to function and participate depends on adaptations to optimize the person-environment fit. Two key concepts in the model of aging well are *belonging* and *agency* (Wahl et al. 2012). Belonging is the experience of a positive connection with other people and the physical environment that can be considered in terms of one's feeling of being who one wants to be and where one wants to be. Agency refers to controlling changes in one's own life by intentional and proactive behaviors and can be thought of as one's feeling of doing what one wants to do. Aging well is manifested in terms of outcomes related to identity, well-being, and autonomy. The importance of the physical and social environment for older adults with ARHI is being increasingly recognized. Crucially, participation depends on interactions between the person and their environment(s) and interventions must be designed to include environmental factors if they are to optimize functioning and promote aging well.

Although exact figures vary around the world, the vast majority of older adults live in their own homes. Those who live in assisted-living facilities may have a number of serious health conditions and it is not surprising that a very high prevalence of HI is reported for such populations. For example, Hopper et al. (2016) reported that 92% of 36 adults with dementia living in aged care had mild or worse HIs. Jee et al. (2005) found that 50.5% of 188 participants living in aged care facilities had moderate-to-severe hearing impairment. In a review of health information data collected from 2009 to 2014 in Ontario, Canada where government funding is available for those who are eligible for home care or long-term care, 63% of 291,824 older adults receiving home care services and 50% of those residing in long-term care facilities were identified as having hearing problems (Guthrie et al. 2018). Notably, 21% of those receiving home care and 29% of those residing in long-term care were identified as having combined hearing, vision, and cognitive impairments. Those with all three impairments were most likely to report loneliness, have reduced social engagement and less independence in activities of daily living. Moreover, communication challenges were noted for 38% of those receiving home care and 50% of those residing in long-term care facilities. In older adults with such complex health conditions, it can be difficult to isolate the effects of their HI on everyday life. However, a qualitative study by Pryce and Gooberman-Hill (2012) provides

valuable insights. These researchers observed and interviewed 18 residents with HI in two aged care facilities and found that their social opportunities were limited because their hearing difficulties restricted participation in structured group activities such as games and puzzles. Compared to living alone at home, there may be more opportunities for social interaction when older people reside in care facilities. However, noise in residential environments, such as cafeteria noise, can disrupt communication and there may be limited opportunities for social participation as a result (van Hout et al. 2014). Thus, both physical and social aspects of living environments affect communication and should be considered when interventions are planned.

In residential care environments, support for people with HI could come from facility staff. Although staff typically express a commitment to provide support to nursing home residents with HI and a desire to improve their skills to do so (Pryce and Gooberman-Hill 2013; Solheim et al. 2016), the evidence is that they are less likely than family members to take a proactive approach (e.g., Pryce and Gooberman-Hill 2012). Importantly, however, when communication is considered in care planning for residents in long-term care facilities, benefits have been shown for residents' quality of life as well as nursing staff's feelings and mood (McGilton et al. 2017), suggesting that improvements in care can be achieved when communication needs are addressed.

Whether older adults continue to live independently in their own homes or receive home care or reside in care facilities, communication is a two-way process and older adults with HI are likely to experience fewer activity limitations and participation restrictions if they have support from their communication partners. In one study, spouses of older adults with HI described having to constantly adapt their communication by using communication strategies, by thinking about the other person's HI, and by protecting their partner with HI from conversation breakdowns (Scarinci et al. 2008); one spouse said: "*I try to face him so he can read my lips. He spends a lot of time in the garden and I'll always have to go right up and talk to him. It's no good trying to have a conversation across the garden.*" Similarly, adult children provide support to their parents with HI as described by Preminger et al. (2015); for example, adult children said they used coping strategies like putting more effort into communication: "*What I do is, I say mom, "look at me" and then I talk to her.*" This kind of support helps the person who has ARHI, but it may take a toll on the significant other in the form of third-party disability. Three factors significantly associated with increased risk of such third-party disability were (1) lower relationship satisfaction by the spouse, (2) greater spousal age difference, and (3) greater misperception of his or her partner's hearing disability by the spouse (Scarinci et al. 2012). In more complex cases, caregiver burden may be increased by the frequent communication breakdowns that occur when an older adult with ARHI has cognitive impairment, and possibly also vision impairment, such that the health of the significant other becomes at risk and intervention is needed for both the person who has impaired hearing and their significant other(s). There is promising evidence, however, that hearing care, even for those who have combined HI with

dementia, can be beneficial to older adults and also their caregivers (Palmer et al. 1999; Dupuis et al. 2019).

11.3 Interventions

A number of intervention options are available for adults with ARHI and their families. The first step is goal-setting using tools such as the Client-Oriented Scale of Improvement (COSI; Dillon et al. 1997) to facilitate this process. What would the person with ARHI like to achieve in treatment? What is most important to him or her? The Goal Partnership Strategy (GPS; Preminger and Lind 2012) is a tool for setting shared goals for both the person with HI and his or her family.

Once goals are set, shared decision-making between the person and clinician is recommended as the most appropriate approach to presenting intervention options so that informed decisions can be made that take into account not only the individual's impairment, but also activity, participation, as well as personal and environmental contextual factors (Laplante-Lévesque et al. 2010a, b). Shared decision-making can be facilitated with the use of decision aids that provide a structure for the presentation of options. Examples of decision aids for older adults with ARHI (Laplante-Lévesque et al. 2010a, b) and for people with tinnitus (Pryce et al. 2018) have been developed and evaluated. A decision aid is in written form and the clinician uses it as a guide to verbally describe what is involved in any particular choice (e.g., number of appointments, cost, support needed from others) and what the evidence is regarding each choice (e.g., benefits, advantages, disadvantages).

11.3.1 Interventions at the Impairment Level

Many avenues for intervention in ARHI have been pursued, including recent pharmaceutical methods (e.g., Frisina and Frisina 2013; Frisina, Chap. 12), but most established interventions include the use of some type of technology. In terms of the ICF, technological interventions for ARHI focus on the body structure and function domain, with the primary aim being to increase the audibility and clarity of sound.

Hearing aids are the most commonly used technology, but there is an increasingly wide array of devices available today for those with ARHI. Some older adults may benefit from cochlear implants, both conventional and short-electrode or hybrid devices (Gifford et al. 2010; Woodson et al. 2010). Multicenter randomized control trials have established the efficacy of cochlear implants in older adults (Gantz et al. 2016; Roland et al. 2016). There is also a similar level of evidence supporting the benefits of assistive listening devices to older adults with ARHI (Yueh et al. 2001). Nonetheless, whereas the numbers of older adults who have received cochlear implants or who regularly make use of assistive listening devices are likely in the hundreds or thousands, those using hearing aids number in the tens of millions in

the United States (Kochkin 2000, 2009) and across the developed world (Hougaard and Ruf 2011; Bisgaard and Ruf 2017). Accordingly, this chapter focuses on hearing aids. It should be noted, however, that what has constituted the "conventional hearing aid" has changed over several decades and continues to do so. There is also a burgeoning number of accessories, such as remote microphones, or software-based tools, such as Apple or Android apps, to augment the functional capabilities of the "conventional hearing aid." In addition to considering the auditory needs of older adults with ARHI, audiologists must consider which recent and future advances may be most useful to older adults with comorbidities and which options may be optimal for use by significant others or caregivers (Dupuis et al. 2019). Furthermore, it is important to note that the delivery and fitting of devices is just one component of a broader approach to intervention and merely reducing impairment will not necessarily address the activity limitations and participation restrictions experienced by the older adults in all contexts (Meyer et al. 2016).

11.3.1.1 Hearing Aids

In the United States, approximately two-thirds of the nearly 4 million hearing aids sold in 2017 went to those 60 years of age and older (Strom 2018). Of those devices, 82.8% were behind-the-ear (BTE) style, with the majority (69.4%) being mini-BTE open-fit devices with the receivers either in the ear or in the canal (Strom 2018). The distribution of types of hearing aids sold in the United States, roughly 80% BTE and 20% in-the-ear, has been stable for about a decade.

All too often, people have the misleading impression that hearing devices restore hearing to normal like glasses restore vision to 20/20 in older adults with presbyopia. Refractive errors of the lens of the eye can be corrected by glasses. Refractive errors may be more like conductive HIs than ARHI. In contrast to presbyopia, sensorineural HI is not fully or quickly corrected, even though there is evidence that benefits from hearing devices are measurable and meaningful in terms of improvements to communication. Beyond peripheral sensorineural damage, there can be changes in the auditory nervous system in ARHI. Compensatory brain plasticity accompanies the gradual progression of age-related auditory declines (Pichora-Fuller 2020). Not surprisingly, it takes months for a person to relearn how to listen using hearing devices and individual differences in relearning may depend on numerous factors, including cognition (Ng et al. 2014). Given sufficient time and listening experience, conventional hearing aids may provide a reasonable solution for the approximately two-thirds of older adults whose speech-communication problems are largely due to the inaudibility of speech sounds. When well fit, conventional hearing aids should restore the audibility of previously inaudible speech sounds while also ensuring that no amplified sounds are uncomfortably loud. However, well-fit hearing aids alone may be insufficient to address the communication problems of a significant portion of older adults.

Candidacy for hearing aids has often been based on pure-tone audiometry, including the 4fPTA that forms the basis of the WHO-new HI grade system. This approach is convenient and data such as those shown in Figs. 11.5 and 11.6 appear to support this notion. Nevertheless, it is well known that individuals with the same 4fPTA may not self-report the same disability, as was shown in Fig. 11.7 for HHIE-S results. Furthermore, although recent approaches to screening HI based on speech-in-noise measures, such as digit-triplet tests (Smits and Houtgast 2005; Watson et al. 2012), are more directly tied to everyday communication than pure-tone audiometry, they still may not reflect underlying activity limitations or participation restrictions experienced by those with ARHI (Mick and Pichora-Fuller 2016). Recognizing the limitations in relying solely on pure-tone audiometry, screening for ARHI has typically added a self-report measure (Ventry and Weinstein 1983; Lichtenstein et al. 1988). Severity of HI, a metric of bodily or sensory impairment, is clearly an important determiner of perceived activity limitations and participation restrictions, but other factors contribute as well. Moreover, even if older adults could benefit from hearing aids, many do not use them.

11.3.1.2 Hearing Aid Uptake and Usage

Figure 11.8 depicts the number of older adults worldwide with "disabling" HI and estimates of hearing aid outcomes for them in terms of hearing aid uptake, retention and satisfaction. About 165 million older adults worldwide have disabling HI ("moderate" or worse 4fPTA). Based on a variety of information sources for the United States and Europe pointing to "uptake" or "market penetration" of about 20% (Hougaard and Ruf 2011; Dawes et al. 2014), it is estimated that about 33 million of the older adults worldwide with "disabling" hearing loss have tried hearing aids. Of those who have tried hearing aids, 28 million are estimated to have kept them (assuming a retention rate or 85% given that a 15% return-of-credit rate is common in the United States after the trial period), even though some buyers may use their hearing aids as infrequently as less than 1 hour per day (Kochkin 2000; Aazh et al. 2015). Finally, 20 million older adults are estimated to be satisfied with their hearing aids based on findings that 70% of those who kept their hearing aids after the trial period reported being satisfied with their hearing aids. The estimate that 20 million people are satisfied hearing aid users is less than 12% of the 165 million older adults with ARHI. Of course, the prevalence of hearing aid use increases as the prevalence of and degree of ARHI increases with age. Chien and Lin (2012) found that the prevalence of hearing aid use in the United States increased from 4.3% in individuals 50–59 years old to 22.1% in individuals who were 80 or more years old. Clearly, based on such limited uptake, the needs of most adults with disabling ARHI are not being met by hearing aids, even in the oldest age group who have the most HI.

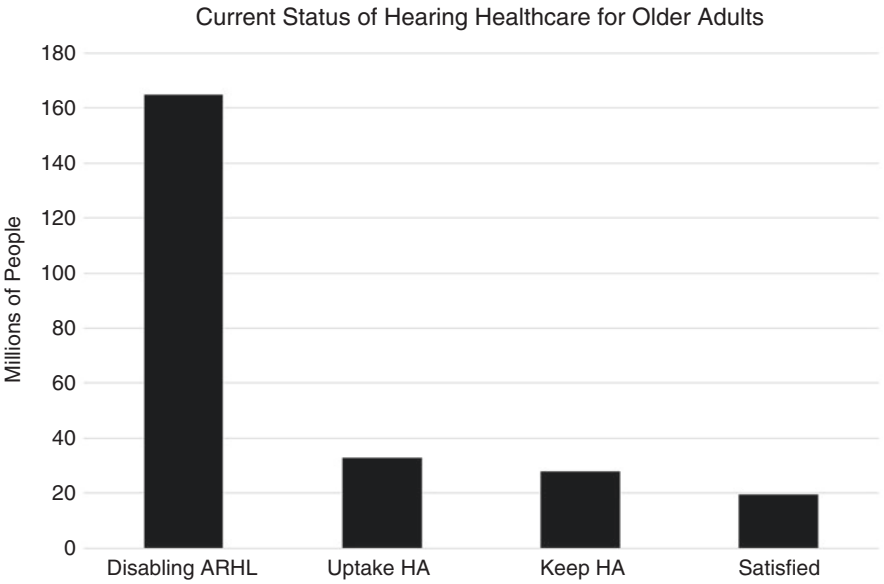

Fig. 11.8 A depiction of the number of older adults worldwide with "disabling" hearing as estimated by the WHO (165 million people) and estimates of hearing aid outcomes for them based on the literature. Uptake was assumed to be 20%, resulting in 33 million people. Retention of hearing aids by those who take them was estimated at 85% yielding 28 million people. Satisfaction among those persons with their hearing aids was estimated at about 70%, yielding 20 million people. The 20 million people who sought hearing aids, kept them and were satisfied with them represents about 12% of the original 165 million older adults with disabling hearing impairment

11.3.1.3 Efficacy of Hearing Aids

Perhaps there is poor uptake and daily usage of hearing aids because hearing aids don't actually provide benefit to older adults with ARHI. There have been few randomized clinical trials studying outcomes from hearing-aid intervention in older adults (Ferguson et al. 2017). To date, the only placebo-controlled randomized clinical trial was conducted in the United States with a total of 154 older adults completing that trial (Humes et al. 2017), followed by a similar smaller scale trial in another group of 40 older adults (Humes et al. 2019). Of the 179 first-time hearing-aid users in the two studies, 174 were categorized as being in the "slight/mild" ($N = 102$) or "moderate" ($N = 72$) WHO-new HI grades. At study completion, all 174 participants were fitted using audiologist-based best practices, including real-ear measurements for fine-tuning the fit and counseling about the use of the hearing aids. Figure 11.9 shows the means and standard deviations for four different hearing-aid outcome measures. The means for placebo devices included in these two studies are indicated by the red "P" symbols in Fig. 11.9 and the asterisk above each set of vertical bars indicates significant ($p < 0.05$) between-group differences.

Several observations can be made from these data. Differences between the treatment and placebo groups were apparent on three of the four outcome measures

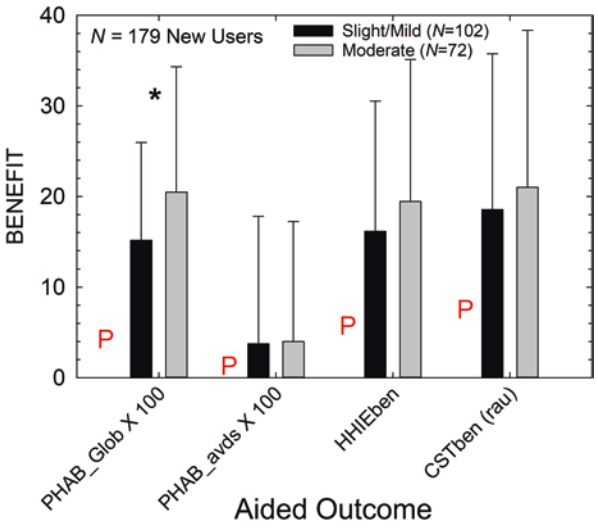

Fig. 11.9 Summary of outcomes for 179 new hearing aid wearers with ARHI for data pooled from Humes et al. (2017, 2019) following audiology best practice service provision. The fill colors for the vertical bars represent the means and standard deviations for those in the "mild" and "moderate" WHO-new HI grades. For reference, red "P" symbols depict the mean outcomes for participants who were fit with placebo hearing aids. In all cases, the outcomes for appropriately fitted hearing aids exceed those from placebo devices. PHAB_Glob, global subscale score from the PHAB; PHAB_avds, subscale score from the Aversiveness and Distortion PHAB scales; HHIEben, difference between aided and unaided scores on the Hearing Handicap Inventory for the Elderly; CSTben, differences between aided and unaided scores on the Connected Speech Test (CST), a sentence-based test of speech-recognition in competing babble

shown in Fig. 11.9; all except PHAB_avds. PHAB_Global is the average of the five subscales of the Profile of Hearing Aid Benefit (PHAB; Cox and Gilmore 1990) that pertain to communication. For this global outcome measure, the measured benefit for the "slight/mild" and "moderate" WHO-new HI groups differed significantly ($p < 0.05$), but this was not the case for the other two benefit measures in Fig. 11.9 (HHIEben, CSTben). In summary, the results from these carefully controlled clinical trials, when analyzed by WHO-new HI grade, reveal that significant benefits can be realized by older adults with ARHI from bilateral hearing aids delivered using audiologist-based best practices. The efficacy of hearing aids in ARHI was established by the finding of measurable benefits in a variety of hearing domains, whether based on speech-recognition scores or self-report surveys of communication function. Importantly, this is true for *both* "slight/mild" and "moderate" WHO-HI grades and for first-time hearing-aid users.

Interestingly, only the "moderate" group would meet the WHO-new HI definition of "disabling" HI based on pure-tone thresholds. Clearly, those without pure-tone-defined "disabling" HI can benefit from intervention with hearing aids. Thus, it would not appear that the lack of measurable benefits is a reason for the poor uptake and use of hearing aids by older adults, regardless of their degree of HI. This

suggests that compensating for the loss of bodily function alone, in this case ARHI, is likely insufficient to address the broader needs of those with ARHI. Consistent with the holistic WHO ICF framework, contextual and environmental factors must also be considered.

11.3.1.4 Contextual Factors Influencing Hearing Aid Uptake and Usage

Several studies have been conducted to identify the factors underlying both the low uptake and the low usage of devices that have been acquired by older adults (see reviews: Knudsen et al. 2010; Meyer and Hickson 2012). Regarding uptake, factors found to positively influence older adults' help-seeking and their subsequent decision to at least try hearing aids are self-reported hearing activity limitations and participation restrictions, increasing age, positive attitudes to hearing aids and support from significant others. Stigma associated with HI and the visibility of hearing aids have also been implicated as possible factors (Southall et al. 2010; Wallhagen 2010). Regarding the frequency of usage for those older adults who have taken up hearing aids, a wide range of factors have been studied. Difficulty handling the devices, perhaps due to dexterity challenges or low self-efficacy; lack of perceived need for hearing assistance; less than desired benefits, especially for speech communication in noisy backgrounds; and lack of family support have often emerged as contributing factors to less than optimal outcomes of hearing aid fitting for some adults (Humes et al. 2003; Hickson et al. 2014).

Features of the hearing healthcare system within which hearing aids are delivered may also contribute to low rates of hearing aid uptake. Summarizing the findings of an NIDCD/NIH working group in the United States, Donahue et al. (2010) argued that there were at least two key factors limiting uptake of hearing aids by older adults: poor accessibility and affordability. In the United States, older adults were deemed to face many barriers, including the need to be assessed by a professional to determine if hearing aids are an appropriate option. In addition, the average cost of hearing aids was beyond the means of many older adults and/or was greater than the perceived benefits to be gained. Such deliberations provided the impetus for reports by the President's Council of Advisors in Science and Technology (PCAST 2015) and the National Academies of Science, Engineering and Medicine (NASEM 2016). These reports suggested that a consumer-decides over-the-countermodel of hearing aid provision in the United States would address both the limited accessibility and poor affordability of hearing aids for older adults.

The issues of limited accessibility and poor affordability vary across countries and health care systems, but variants of these issues may be relevant beyond the United States. In the developing world, for example, access to and affordability of hearing healthcare and hearing aids represent major problems for all people who have HI, including older adults with ARHI. In response to the needs of older adults in the developing world, self-fitting hearing aids have been developed (Keidser and Convery 2016, 2018). These devices allow pure-tone audiometry to be performed through the device and then the results are used to automatically program the gain

and output of the device. Furthermore, the electroacoustic performance of the devices can be modified based on intelligent analyses of the wearer's sound environment and listening patterns over time. For current self-fitting devices, however, the fitting process is not entirely automated. For example, the physical coupling of the device to the wearer's ears must be completed manually by the wearer and maintenance of the device and optimization of its use by the wearer still require participation by the wearer. Research is ongoing regarding factors that lead to the successful use of self-fitting hearing aids (Convery et al. 2017).

Can older adults with ARHI select and fit their own hearing aids and achieve positive outcomes? This question was the focus of the previously mentioned (Sect. 11.3.1.3) placebo-controlled clinical trials by Humes et al. (2017, 2019). Figure 11.10 shows the main results in terms of measured benefit, either based on self-report surveys or speech-recognition testing, with unaided performance measured before and aided performance measured after a 5-to-6-week trial period. The means and standard errors are plotted for the placebo (P), consumer-decides (CD) and audiology-based best-practices (AB) groups. The CD service-delivery model made use of instructions for self-fitting hearing aids from Caposecco et al. (2011). The short horizontal lines above the sets of three bars for each outcome measure show the significant ($p < 0.05$) between-group differences observed. PHABavds was expected to yield near-zero values and group differences were not expected. For the other three outcome measures shown in Fig. 11.10, the benefit measured for the AB and CD groups significantly exceeds that measured in those using the placebo (P).

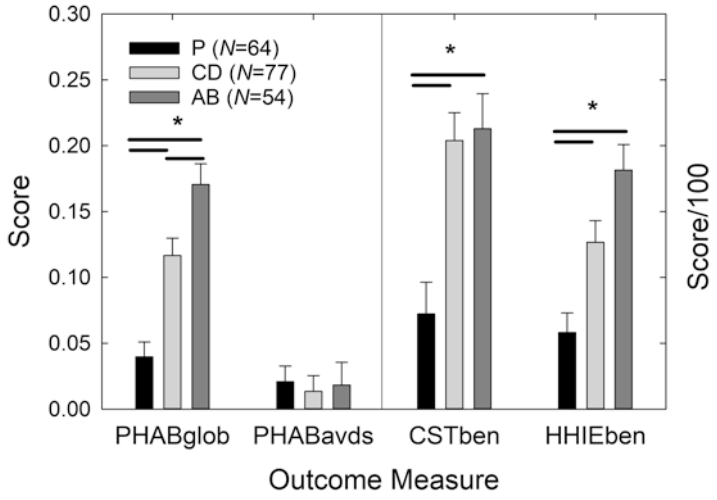

Fig. 11.10 Outcomes for 195 older adults with ARHI who were new hearing aid users in the studies of Humes et al. (2017, 2019). Three groups are shown here: Placebos (P), Consumer Decides (CD), and Audiologist Based (AB). The placebos served as controls in both studies and the other two groups differed in the way the hearing aids were provided to the older adults: either via audiology best practices (AB) or self-selection by the older adult (CD). The heavy horizontal lines above the vertical bars depict significant differences in paired comparisons

Further, for two of the three measures, speech-recognition (CST) benefit and HHIE benefit (HHIEben), there were no significant differences in benefit between the CD and AB groups. For the other measure (PHABglobal), the benefit measured in the AB group exceeded that of the CD group. It should be noted, however, that when those initially in the CD and P groups were subsequently provided with AB services and reevaluated, the measured outcomes were often significantly ($p < 0.05$) better following AB service-delivery (Humes et al. 2017, 2019). More research is needed, but it appears that older adults who are first-time hearing aid users can self-select hearing aids and obtain positive outcomes.

Self-fitting hearing aids are one of several ways in which hearing aids of the future may be delivered directly to older adults with ARHI, possibly improving the accessibility and affordability of hearing aids. Recent research on self-fitting hearing aids has further illustrated the importance of considering matters such as techniques for fitting hearing aids and the acoustical factors, such as the severity of HI, when determining the possible benefit of such devices (Convery et al. 2017). In any case, whether hearing aids are self-fitting or are delivered by traditional methods, the solutions provided by technology will address primarily the impairment level, but technology alone is unlikely to address the needs of older adults with ARHI at the activity and participation levels.

11.3.2 Interventions at the Activity and Participation Levels

Traditionally, nontechnological rehabilitation for people with hearing disability has involved communication training focused on auditory or speechreading training, often using simplified speech materials in highly structured training procedures (Pichora-Fuller and Levitt 2012). Variants on this sort of training have been implemented in software algorithms so that individuals could use computers to engage in training at home, at their own pace, and at lower cost. Unfortunately, the results of a randomized control trial to evaluate one of the more promising recent computer-based training programs, *Listening and Communication Enhancement* (LACE; Sweetow and Sabes 2006, 2010), found that the intervention was no more effective than a placebo program (Saunders et al. 2016b), a finding consistent with the broader body of research on the effects of auditory training in ARHI (Henshaw and Ferguson 2013). A highly structured approach to training often fails because it is not tailored to the needs of the individual, individuals are not sufficiently motivated to spend enough time training, and task- or material-specific improvements do not generalize readily to everyday communication. Some approaches that are more likely to result in improvements at the activity and participation levels of functioning include communication education programs to promote self-management of ARHI-related disability, psychosocial interventions to facilitate adjustment to hearing loss by increasing self-efficacy or reducing stigma, or cognitive training to enhance performance in more realistic multitasking conditions.

11.3.2.1 Communication Education

Older adults with ARHI and their communication partners can benefit from education about strategies to improve their ability to communicate optimally in everyday life. Such education can either supplement or be an alternative to hearing device fitting for those who are not ready for, or cannot afford, devices (Hickson and Worrall 2003). Laplante-Lévesque and her colleagues (2012) used a decision aid to present 153 older adults seeking help for the first time with options of hearing aid fitting, communication education or no action. Six months after the initial choice was made, 43% had obtained hearing aids, 18% had completed communication education and 39% had taken no action. Thus, communication education was pursued as a first treatment option for approximately one in five older adults.

An example of a well-studied group program for older adults is the *Active Communication Education* (ACE) program (Hickson et al. 2007; Oberg et al. 2014). ACE can also be offered to individuals (I-ACE) (https://shrs.uq.edu.au/active-communication-education-ace). When educating older adults about how to improve hearing and communication in everyday life, the most important strategies are: decreasing background noise during conversations; using audio-visual cues in face-to-face conversations; explaining hearing difficulties to talkers along with suggestions for how to make conversation easier to follow; and effectively repairing conversation breakdowns when they inevitably occur. Such education uses a problem-solving approach that encourages participants to identify the source of a communication difficulty, develop strategies to overcome the difficulty and practice the skills necessary to undertake the strategy. In a systematic review, including meta-analysis of 10 studies of group communication education, outcomes provided evidence that participants in these programs achieved improved participation in everyday life (Chisolm and Arnold 2012).

11.3.2.2 Social Psychological Interventions

As discussed in Sects. 11.3.1.1 and 11.3.1.2, social psychological factors are key to understanding why many older adults who are candidates for hearing aids do not pursue or benefit from technological interventions to address the impairment level of ARHI. Applying theories from health psychology, new measures and therapeutic approaches have emerged that target changes in attitudes, motivation and behaviors to help adults adjust to living with hearing loss (Coulson et al. 2016; Saunders et al. 2016a). An overview of how various social psychological factors may influence participation (Pichora-Fuller 2016) includes stigma and self-efficacy as two issues that may be addressed in interventions for people with ARHI.

In a review of factors affecting help-seeking for hearing loss, stigma was recognized to be one of the main reasons for delayed uptake and limited use of hearing aids by older adults (Knudsen et al. 2010). Stigma is a negative stereotype that may be held by others or the self. Discriminatory behaviors and prejudices can be rooted in such stereotypes. Treatment uptake and outcomes for those with ARHI could be

affected by stigma specific to hearing disability (Gagné et al. 2009). In addition, stigma to age can trigger biased treatment of older people as well as negative self-perceptions of aging among older adults themselves (Chasteen 2018). In a scoping review of research on stigma associated with hearing loss and hearing aids, 14 of the 21 papers that were reviewed examined self-stigma, with nine of these papers reporting results linked to age or ageism (David and Werner 2016). Older adults often express opinions about hearing aids that reveal how their negative views of aging can impede the uptake of hearing aids (e.g., *I don't want to use a hearing aid because it will make me look old*) and/or undermine the use of and benefit from hearing aids (e.g., *I'm too old to start using a hearing aid*). Furthermore, older adults' stereotypes of aging predict declines in hearing (Levy et al. 2006). In a study of about 300 older adults from the community, negative views of aging were associated with poorer self-perception of hearing ability which was associated with poorer performance on hearing tests (Chasteen et al. 2015). Thus, as well as being a barrier to hearing healthcare, negative views of aging may even be a risk factor for age-related hearing decline. Some studies have reported less stigma in hearing aid wearers compared to nonwearers (Erler and Garstecki 2002), and questionnaires to evaluate stigma to hearing loss have been developed (Vincent et al. 2017), but research on interventions to counteract the deleterious effects of stigma for people with ARHI is lacking (David and Werner 2016).

Self-efficacy refers to domain-specific "beliefs in one's capabilities to organize and execute the courses of action required to produce given attainments" (Bandura 1997, p. 3). Individuals with high self-efficacy tend to cope better, expending greater effort to achieve a target behavior and persevering despite difficulties (Bandura 1997). Self-efficacy contributes to the successful management of a wide range of health conditions. Some progress has been made in developing measures and interventions targeting self-efficacy in the interventions for ARHI. Measures of self-efficacy have been developed for hearing aid use (Smith and West 2006b), listening (Smith et al. 2011), and managing communication situations (Jennings et al. 2014). Methods for enhancing self-efficacy in interventions for people with ARHI have been described (Smith and West 2006a), but research is needed to examine their effectiveness.

Low self-efficacy may be exacerbated by stigma and negative attitudes and both may increase stress and reduce motivation to pursue interventions. A feasibility study of an intervention to increase motivation in first-time hearing aid users suggests that there may be benefits but further research is needed (Ferguson et al. 2016). Evidence from other health domains has kindled interest in the potential benefit of interventions for people with ARHI that target social psychological factors such as stigma, self-efficacy, and motivation. However, the implementation of successful interventions will no doubt rely on the development of a more comprehensive model of how these social psychological factors influence each other and change with age as HI and other comorbidities reduce the capacity of older adults to confront everyday functional demands as they engage in activities and participate (Pichora-Fuller 2016).

11.3.2.3 Cognitive Intervention

Listening, comprehending, and communicating are essential to participation in many everyday situations and they depend on both auditory and cognitive processing (Kiessling et al. 2003; Pichora-Fuller et al. 2016). According to the cognitive compensation hypothesis (Li and Lindenberger 2002), to maintain functioning that is compromised by sensory and/or motor declines, older adults compensate by recruiting cognitive resources. For example, falls may occur when the limits of compensation are reached because older adults with declines in multiple sensory and/or motor domains (hearing, vision, balance) do not have sufficient cognitive resources to contend with the demands of functioning when participating in complex everyday activities (Bruce et al. 2017; Li et al. 2018). Cognitive training interventions based on the cognitive compensation hypothesis have been developed recently by psychologists using dual-task training to target processes such as dividing attention and inhibiting responses to distraction, with preliminary evidence suggesting that cognitive training could benefit older adults with ARHI (Bruce et al. 2019). Conversely, interventions developed by audiologists have demonstrated that auditory training can improve cognitive performance on measures of working memory, attention, and communication in adverse listening conditions for older adults with ARHI (Ferguson and Henshaw 2015). Nevertheless, a recent systematic review of nine studies reported that, while significant positive effects on cognition were observed for auditory, cognitive, and combined auditory–cognitive interventions, more research is needed because the effect sizes were small for auditory training and very small for cognitive training (Lawrence et al. 2018). Importantly, compared to traditional approaches to training, multidomain interventions that more closely approximate realistic conditions and address contextual factors could generalize more readily to improvements in the quality and quantity of participation in everyday life by older adults with ARHI. Furthermore, multidomain approaches are promising insofar as psychosocial factors such as stigma and self-efficacy may affect both auditory and cognitive functioning in everyday life (Pichora-Fuller 2016).

11.3.2.4 Environmental Interventions

As depicted in the WHO ICF (see Sect. 11.2.3.2), physical and social environmental factors can be barriers to or facilitators of participation. It is important to optimize the person-environment fit so that older adults can age well and achieve their participation goals. Although hearing aids can be effective in addressing HI, it is reasonable that interventions targeting mismatches between the person with ARHI and their social and physical environments are more likely to be effective in addressing the emotional, social, and cognitive consequences of aging with ARHI.

Interventions targeting the social environment of people with ARHI are much less developed than are the typical technological interventions dominated by hearing aid fitting. Nevertheless, interventions that include communication partners can benefit the person with ARHI by promoting social support on the part of

communication partners (Singh et al. 2015). In addition, communication partners experiencing third-party disability (Sect. 11.2.2.1) can also benefit when their views are taken into consideration during goal-setting and shared decision-making in rehabilitation (Scarinci et al. 2013). Some interventions provide training in communication and conversational strategies for communication partners (Erber and Lind 1994). Newer family-centered care approaches (Singh et al. 2016) address social environmental factors using counselling techniques to provide an opportunity for families to engage in a discussion of their feelings and opinions about priorities for hearing care (Ekberg et al. 2015).

Interventions targeting the physical environment may be difficult to address within the confines of institutions, but such interventions have sometimes been incorporated into audiologic rehabilitation, especially for older adults living in residential care where mismatches in the person-environment fit are apparent. When potentially beneficial environmental modifications are identified and the institution is willing to design new spaces or renovate existing spaces, other professionals such as architects or acoustical consultants provide the expertise to implement physical environment solutions. Acoustical standards for the physical environment, including healthcare facilities, now provide targets for optimizing communication environments (Facility Guidelines Institute 2014a, b).

Beyond interventions undertaken by hearing healthcare or other professionals working with individuals with ARHI or their families, universal approaches to hearing and communication accessibility can now be undertaken by implementing social policies following the WHO Global Age-friendly Cities Guide (WHO 2007). These policies mobilize changes spanning a wide range of both social and physical environmental factors at the community level. Importantly, such initiatives to promote hearing health are situated within the broader context of initiatives to promote aging well (WHO 2015; Davis et al. 2016).

11.4 Chapter Summary

This chapter began with an overview of the effects of aging on the peripheral auditory system, focusing on the direct consequences of this impaired bodily function for speech communication. Using the WHO ICF, ARHI was considered in terms of its effects on the everyday function of older adults, including limits on activities and restrictions on older adults' participation in society. In this broader context, impaired hearing is an extremely important contributor to everyday difficulties experienced by older adults, but it must be placed in the context of other age-related changes in sensory and cognitive function and relevant comorbidities. It is clear that interventions aiming only at remediation of auditory problems will most likely not yield the intended benefits in everyday function. Technologies should be considered a part of the solution, but not the complete solution. Recognition of the broader context for the everyday difficulties experienced by older adults with impaired hearing requires that intervention research be positioned in a broader context as well. Multidisciplinary

research involving interprofessional collaborations to address the needs of the whole person is critical if interventions are to succeed in helping older adults with ARHI to age well. Disciplines and professions addressing the auditory, visual, physical, cognitive, social, and emotional aspects of aging must collaborate more in research and in clinical practice if intervention is to prove successful in minimizing the activity limitations and participation restrictions experienced by older adults, including those with ARHI. In the future, older adults with ARHI may benefit from changes in the hearing healthcare system to foster interprofessional care and in social policies to promote age-friendly communities that are more accessible.

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Chapter 12
Emerging Clinical Translational Treatment Strategies for Age-Related Hearing Loss

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Abstract Recent advances in audiological research, biomedical and chemical engineering, and hearing sciences suggest that effective biomedical treatments, technological interventions, and acoustic-based therapies will soon bring some exciting opportunities to delay or treat key aspects of age-related hearing loss (ARHL), or presbycusis. In the present chapter, some of the provocative research that is paving the way for these upcoming successful interventions, including the groundwork for a first FDA-approved drug or system to treat acquired hearing loss, including age-related, is presented. Impactful work on drug and medicinal discover-

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ies and developments; localized drug delivery possibilities, including micropumps and hydrogels; and acoustic/technological approaches for effective interventions are highlighted in the present chapter. In the same way that cochlear implant development has been remarkable in the past decades, starting with the initial one-channel cochlear implants developed and tested early on at the House Ear Institute, we will soon experience remarkable breakthroughs for interventions to prevent or treat presbycusis.

Keywords Auditory drug development · Auditory hormone therapies · Auditory training · Augmented acoustic environment · Cochlea therapies · Cochlear micropumps · Ear hydrogels · Inner ear treatments · Sound therapies

12.1 Introduction

The field of hearing loss and deafness research and rehabilitation is on the cusp of dramatic new technological and drug prevention and treatment breakthroughs. Strategies for preventing, slowing down, or reversing the deleterious perceptual characteristics of age-related hearing loss (ARHL; a full list of abbreviations used in this chapter is provided in Table 12.1), or presbycusis, are quite provocative and exciting. This chapter summarizes the pros and cons of different clinical and translational approaches. As there are still no Food and Drug Administration (FDA)-approved drugs for treating ARHL, or any other type of acquired hearing loss, this is a particularly active and fast-moving area of research and development by both academic and clinical researchers and research and development (R&D) teams at hearing aid and pharmaceutical companies. Examples of drug and compound development, and technological device and training paradigms will be highlighted.

12.2 Chemical and Drug Approaches

Only a minority of aging persons use hearing aids on a regular basis. So, there is strong motivation to develop drugs to treat ARHL or to enhance the performance of hearing aids. Building upon molecular mechanism and anatomical studies of presbycusis (as covered in other chapters of this volume, such as those by Someya and Kim, Chap. 2; Ohlemiller and Spankovich, Chap. 3; Syka, Chap. 4; and Recanzone, Chap. 5), academic and industrial groups have developed drugs that yielded preclinical evidence from animal model investigations providing data supporting the efficacy of slowing down the progression of ARHL, or preventing some of its key

Table 12.1 Abbreviations used in this chapter

AAE	augmented acoustic environment
ABR	auditory brainstem response
ADD	attention deficit disorder
ALD	aldosterone
ARHL	age-related hearing loss
ASR	acoustic startle response
AVCN	anteroventral cochlear nucleus
CN	cochlear nucleus
CS	contralateral suppression
DCN	dorsal cochlear nucleus
DEX	dexamethasone-21-phosphate-disodium salt
DPOAE	distortion-product otoacoustic emission
E	estrogen
EP	endocochlear potential
FDA	Food and Drug Administration
HINT	Hearing-In-Noise Test
HRT	hormone replacement therapy
IC	inferior colliculus
IGF-1	insulin growth factor-1
IHC	inner hair cell
LACE™	Listening and Communication Enhancement
MCR	mineralocorticoid receptor
MNTB	medial nucleus of the trapezoid body
MOC	medial olivocochlear
NKCC	Na^+-K^+-Cl^- cotransporter
OHC	outer hair cell
PPI	prepulse inhibition
PTA	pure-tone audiometry
PVCN	posteroventral cochlear nucleus
RNS	reactive nitrogen species
ROS	reactive oxygen species
SGN	spiral ganglion neuron
SOC	superior olivary complex
TEOAE	transient evoked otoacoustic emission

characteristics. Drug development and clinical testing of the drugs to prevent or treat ARHL will be presented in this section.

12.2.1 Pioneering Explorations of Drugs to Treat Age-Related Hearing Loss

Some creative initial studies were made to investigate drug approaches to prevent or treat ARHL. These approaches received inspiration from studies of the aging nervous system where provocative research started revealing some of the cellular and molecular mechanisms of age-linked disorders, such as mitochondrial dysfunction, calcium regulation toxicities, and posttranslational protein modifications that alter key cochlear ion transporters and other important inner ear macromolecules.

An initial clinical approach was undertaken by Dubno's research group (Mills et al. 2006). They gained some insights in this area by surveying an older group of human subjects, looking for correlations of FDA-approved drug use and severity of ARHL. They administered a questionnaire on medicinal drug use to 357 older adults. Results uncovered gender effects. Specifically, for males, none of the surveyed drugs had any measurable effects on hearing loss, whereas women taking calcium channel blockers had hearing levels 12 dB better than women not taking them. Moreover, women taking β-adrenergic medication had hearing levels 20 dB poorer. Women taking antihistamine/cold preparations had hearing levels 9 dB poorer. Data from 13 additional women using other calcium channel blockers showed hearing levels 10–14 dB poorer than those of age-matched controls. These initial survey findings suggest that drug actions can influence the severity of ARHL, and these data underscore the importance of incorporating sex differences and hormonal considerations into study designs of drug and chemical effects on the progression of ARHL.

12.2.1.1 Age-Related Mitochondrial Dysfunction: Oxidative Stress and Reactive Oxygen Species

Seidman et al. (2002), recognizing the importance of cellular respiration factors in aging, employed lecithin, a polyunsaturated phosphatidylcholine, serving as a high-energy functional and structural element of biological membranes. This compound plays rate-limiting roles in the activation of numerous membrane-bound enzymes, including superoxide dismutase and glutathione, which are important antioxidants protecting cell membranes from damage by reactive oxygen species (ROS). ROS-induced damage to mitochondrial DNA may lead to reduced mitochondrial function in the cochlea and resultant hearing impairment. Seidman et al. (2002) investigated the effects of lecithin on ARHL in rats by measuring auditory brainstem responses (ABRs) and mitochondrial function, an index of aging. Harlan–Fischer rats aged

18–20 months ($N = 14$) were divided into experimental and control groups, where the treated group received lecithin orally for 6 months. ABRs were recorded at 2-month intervals and showed significant preservation of hearing sensitivities in the treated subjects. Flow cytometry revealed significantly larger mitochondrial membrane potentials in the lecithin-treated group, indicating improved mitochondrial functionality. Finally, the common aging mitochondrial DNA deletion [mtDNA(4834)] was assessed from brain and cochlear tissue, including stria vascularis and auditory nerve. This specific deletion was found significantly less frequently in all of these tissues in the treated group relative to the controls. They concluded that lecithin may preserve cochlear mitochondrial function and help protect from hearing loss associated with aging.

Continuing with the theme that damage from ROS linked to mitochondrial dysfunction is a key component of ARHL, the possible roles of agents involved in increasing antioxidants in the cochlea were investigated (Someya et al. 2010). Specifically, it was noted that caloric restriction extends the life span and health span of a variety of species and that there is some animal-model evidence that it can slow the progression of ARHL. It was reported that in mice lacking the mitochondrial deacetylase Sirt3, a member of the sirtuin family, caloric restriction did not slow down the progression of ARHL. In terms of cellular mechanisms, in response to caloric restriction, Sirt3 deacetylates and activates mitochondrial isocitrate dehydrogenase 2 expression, leading to an increased ratio of reduced-to-oxidized glutathione in mitochondria, a cellular response that protects from the negative effects of ROS and oxidative stress, via increased NADPH levels. The findings identified Sirt3 as an essential player in enhancing the mitochondrial glutathione antioxidant defense system during caloric restriction, suggesting that Sirt3-dependent mitochondrial adaptations may be a key mechanism of slowing down aging in mammals.

Tadros et al. (2014) pursued the concept that many aging disorders of the nervous system involve cellular damage from free radicals linked to production of reactive oxygen and/or nitrogen species (ROS and RNS, respectively) and would likely play key roles in ARHL disease progression. The largest study to date of gene expression for ARHL utilizing gene microarrays in mice of different ages was carried out. In particular, antioxidant system gene expression changes were explored, such as glutathione and thioredoxin, which are important systems in the pathophysiology of the aging nervous system. In this investigation, relations between the expressions of antioxidant-related genes in these families were explored in the cochlea, and ARHL was measured by ABRs and distortion-product otoacoustic emissions (DPOAEs) for CBA/CaJ mice. Forty mice were classified into four groups according to age and degree of hearing loss. Cochlear mRNA samples were collected and cDNA generated. Using the Affymetrix GeneChip, the expressions of 56 antioxidant-related gene probes were analyzed. The expressions of glutathione peroxidase 6, *Gpx6*; thioredoxin reductase 1, *Txnrd1*; isocitrate dehydrogenase 1, *Idh1;* and heat shock protein 1, *Hspb1*; were significantly different, or showed large fold-change differences between subject groups. The *Gpx6* gene was upregulated while the *Txnrd1* gene was downregulated with age/hearing loss. The *Hspb1* gene was found to be downregulated in middle-aged animals as well as those with mild presbycusis,

whereas it was upregulated in those with severe presbycusis. These results facilitate development of future interventions to predict, prevent or slow down the progression of presbycusis. However, one of the initial systematic attempts to administer a mixture of antioxidants to aging animals failed to produce a successful result. Sha et al. (2012), using aging mice, showed that there were no significant differences between outcome measures for animals following an antioxidant rich diet compared to control animals.

12.2.1.2 Disruption of Calcium Regulation with Age Can Result in Ca^{2+} Cellular Toxicity

Proper intracellular calcium concentrations are required for normal cellular functions, including effective cellular depolarization in sensory and neural cells and release of neurotransmitters for auditory processing in the inner ear and central auditory system. Improper calcium regulation has been implicated in various age-linked neurodegenerative disorders, so it is likely to play a role in presbycusis. Calcium-binding proteins have buffering properties against calcium overload and could play a protective role during aging. Calbindin, calretinin, and parvalbumin are prominently and differentially expressed in the sensory cells and neurons of the peripheral and central auditory systems (Zettel et al. 1991; Kelley et al. 1992). Zettel et al. (1997) discovered that there were significant declines in calbindin expression in commissural regions of the inferior colliculus (IC), in both CBA/CaJ and C57Bl/6 mice. The CBAs lose their hearing sensitivity slowly over their lifespan like most humans, and the C57s have a rapid, peripheral ARHL driven by a gene that causes an accelerated deterioration of an important hair cell protein (cadherin 23, a calcium-dependent cell adhesion protein). Therefore, C57s, which are genetically similar to a few clinical cases of rapid ARHL, are a valuable animal model for studies of presbycusis, as C57s in their first year of life have an "old" cochlea but still have a young adult brain. This allows ARHL researchers to tease out effects of aging on the inner ear versus effects on the aging brain. Finding calbindin down-regulation in the IC of both of these mouse strains indicated that this down-regulation was likely due to factors in the aging brain, rather than driven by differences in peripheral hearing sensitivity. Surprisingly, Zettel et al. (1997) discovered *increases* in calretinin expression in key areas of the IC, including the dorsal cortex, lateral nucleus and nucleus of the commissure, in the old CBA mice. This increase was unexpected, and in fact was the first report of an increase in calcium binding expression in the aging auditory system, because in most cases of neurodegenerative aging, there is a decrease in calcium-binding protein expression (Ouda et al. 2008, 2012). They interpreted the calretinin increase as a possible compensatory mechanism for the age-linked decrease in calcium regulation due to the declines in calbindin. As the calretinin increased expression was not observed in the old C57s, which were functionally deaf in old-age, it could be that the increase in calretinin in CBAs, which have some residual hearing in old age, is an activity-driven compensation process, where increased neural activity levels require more intracellular calcium regulation.

This idea was later confirmed by Zettel et al. (2001), when they observed significantly higher levels of calretinin expression in old, normal CBAs, versus CBAs that were deafened at a young age, then allowed to survive to old age, i.e., peripheral neural input activity to the IC (outputs of the cochlea) was removed in the deafened CBAs.

Studies at the level of the cochlear nucleus (CN) revealed additional age-related changes in calcium regulation in the central auditory system. Zettel et al. (2003) tested the hypothesis that calretinin levels in the aged mouse auditory brainstem depend on hearing ability for CN neurons. Old animals with good hearing, and thus higher sound-evoked activity levels, were predicted to have higher levels of calretinin immunoreactivity than old animals with hearing loss. Calretinin immunoreactivity was analyzed in the dorsal cochlear nucleus (DCN), including the deep layer (layer III) in CBA/CaJ mice that were normal or bilaterally deafened at 3 months of age with kanamycin, and then aged until 24 months. This manipulation partially mimics the lack of sound-evoked auditory activity experienced by old C57BL/6 J mice, which are deaf at 24 months of age (but show residual hearing at 15 months) and have lower levels of calretinin immunoreactivity than old CBA mice with normal hearing, as presented earlier in this section. Cell counts revealed that the density of calretinin+ cells in DCN layer III of the deafened CBA mice was significantly reduced relative to old intact CBA mice raised under identical conditions.

Canlon's group at Karolinska Institute also explored changes in intracellular calcium regulation by calcium-binding proteins in the CN, focusing on parvalbumin. They looked at changes in these proteins in CBA mice of different ages, and demonstrated that the percentage of calretinin- and parvalbumin-immunopositive neurons in the DCN showed a statistically significant positive correlation with inner hair cell (IHC) loss, outer hair cell (OHC) loss, and spiral ganglion neuron (SGN) declines with age (Idrizbegovic et al. 2001). A correlation was also observed between age, hair cell and neuronal losses, and calcium-binding protein expression in the DCN.

Continuing their exploration of the CN, Canlon's group employed C57BL/6 J (C57) mice (1–30 months old). A rigorous, quantitative stereological method, the optical fractionator, was used to count the total neuron numbers and the number of immunostained neurons in the posteroventral cochlear nucleus (PVCN) and DCN (Idrizbegovic et al. 2004). Using Nissl staining, a statistically significant age-related decline of the total number of neurons was reported in the PVCN and DCN. In the DCN, an age-related increase in the total number of parvalbumin+ neurons was found, while no changes for the calbindin+ or calretinin+ neurons took place. In the PVCN, the total number of positive neurons remained stable for all three calcium-binding proteins with age. The percentage for all three calcium-binding neurons significantly increased in the DCN, and the percentage of parvalbumin+ and calbindin+ neurons increased in the PVCN (Fig. 12.1). These findings imply that there is a relative upregulation of calcium-binding proteins in neurons that had not previously expressed these proteins, or that these neurons are less susceptible to hearing loss. This plastic response in the older, profoundly hearing-impaired C57 mouse

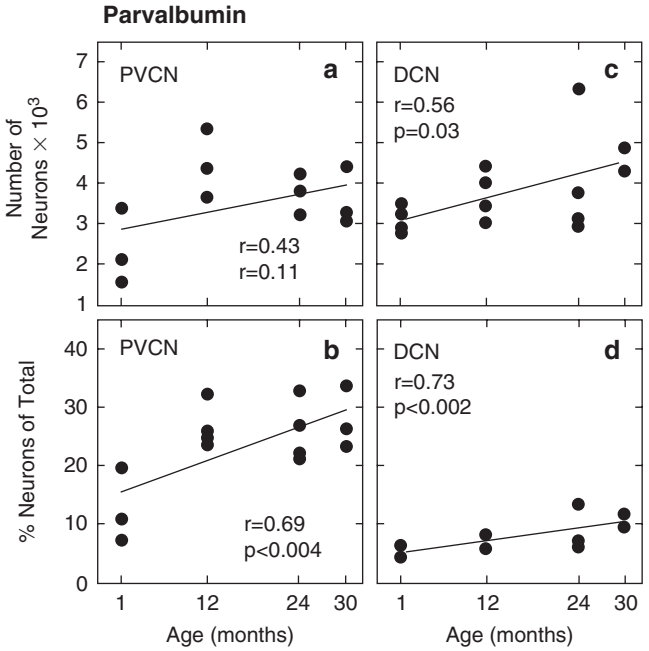

Fig. 12.1 Quantitative analysis of parvalbumin immunoreactivity in the posteroventral cochlear nucleus (PVCN, **a**) and DCN (dorsal cochlear nucleus, **c**) showing no significant difference in the total number of parvalbumin-immunopositive neurons in the PVCN but a significant disparity in the DCN. The percentages of parvalbumin-positive neurons in the PVCN (**b**) and DCN (**d**) show a significant positive regression with increasing age. The points shown are data from individual animals. (From Idrizbegovic et al. 2004, with permission)

may be a survival strategy for CN neurons. Overall, the work of Zettel and coworkers and Canlon's team indicates that the health of the cochlea with age can significantly affect the neural viability and calcium regulation in the CN and IC of the central auditory system during aging. Collectively, these findings regarding age changes in calcium regulation at various levels of the auditory system suggest that a drug or other biomedical intervention to improve cellular calcium regulation with age would improve sensory and neural cell function, and possibly ameliorate key aspects of ARHL. More detail about these concepts can be found in Wildburger et al. (2009).

12.2.1.3 Hormonal Interventions: Sodium and Potassium Regulation in the Cochlea

One research avenue has been to pursue the possibilities of hormonal supplementation for being part of a drug cocktail to slow down the progression of ARHL, including hormones such as aldosterone (ALD) and estrogen (E), which generally decline

with age in mammals (Weidmann et al. 1975). Key inspiration for this line of research came from the examination of some effects of corticosteroid hormones on hearing loss. Trune and colleagues discovered that oral administration of ALD can reverse hearing loss in autoimmune mice, while spironolactone (an ALD antagonist) blocked this effect (Trune et al. 2000, 2006; Trune and Kempton 2001).

The rationale for the ALD line of research and drug development for ARHL is as follows. The endocochlear potential (EP) is critical for maintaining sensitivity of the inner ear. Maintenance of the EP depends on recycling endolymphatic K^+ via the stria vascularis (Salt et al. 1987). K^+ transport occurs via Na^+/K^+ pumps (Na^+/K^+-ATPase) that take up K^+ from the perilymph and extracellular fluid assisted by Na^+-K^+-Cl^- cotransporters (NKCCs) and voltage-gated K^+ channels (Kv; KCNQ1, KCNE1). These ion channels move Na^+ into cells to permit extrusion of K^+ against a voltage and concentration gradient into scala media, thereby generating the EP (Salt et al. 1987). Deficiencies or imbalances between Na^+/K^+-ATPase, Kv channels and NKCC in the cochlea lead to morphological and functional effects on cell populations downstream in the K^+ recycling pathway and to hearing loss (Schmiedt et al. 2002; Spiess et al. 2002; Spicer and Schulte 2005). In this manner, age-related changes in the balance of Na^+/K^+-ATPase, Kv channels and NKCC contribute to presbycusis, consistent with Schuknecht's original concept of strial presbycusis (Schuknecht and Gacek 1993). EP declines can also lead to hair cell and SGN degeneration with age, Schuknecht's sensory and neural presbycusis (Schulte and Schmiedt 1992). ALD is a mineralocorticoid secreted by the adrenal cortex that plays a primary role in controlling serum Na^+ and K^+ levels. ALD regulates expression of both Na^+/K^+-ATPase and NKCC and provides a long-term regulatory effect on Na^+/K^+-ATPase via changes in mRNA/protein synthesis. This regulatory effect is widespread in organ systems of the body and specifically has been shown in the inner ear (Pitovski et al. 1993a, 1993b), as well as the brain (Grillo et al. 1997). ALD can also upregulate NKCC, but the mechanism by which it acts is unclear, as no increase in NKCC1 mRNA has been shown in other (nonsensory) physiological systems (Jiang et al. 2003).

Serum ALD levels decrease with age in humans (Belmin et al. 1994; Mulkerrin et al. 1995) and other mammals, including rodents (Brudieux et al. 1995; Kau et al. 1999). Specifically, mean serum ALD levels in mouse pups are in the 1300 ± 150 pg/ml range (McDonald et al. 1999). In aging mice these mean levels decline, to 900 ± 100 pg/ml (Wang et al. 2004). For ARHL, a correlation was discovered between low serum ALD and severity of presbycusis in elderly human subjects (Tadros et al. 2005). That study went on to examine the role of ALD directly in the regulation of cochlear K^+ transport systems and pathways, its dysfunction with age, and a possible protective effect of maintaining optimal ALD levels in old age.

Ding et al. (2014) conducted the in vitro studies, looking at influences of ALD treatments on human cell lines. Their rationale was that sodium/potassium/chloride cotransporter (NKCC1) proteins play important roles in Na^+ and K^+ concentrations in key physiological systems, including cardiac, vascular, renal, nervous, and sensory systems (Vidal Pérez-Treviño 2011). In addition, NKCC1 expression levels and functionality are altered in some medical conditions and tend to decline with

age. When ALD was applied to a human cell line (HT-29 cells) it was demonstrated that ALD can regulate NKCC1 protein expression, quite sensitively and rapidly, independent of mRNA expression changes (Ding et al. 2014). Utilization of a specific inhibitor of mineralocorticoid receptors (MCRs, the receptors ALD bind to on cell membranes), eplerenone, implicated these receptors as part of the ALD mechanism of action. Further experiments revealed that ALD can upregulate NKCC1 by increasing protein stability, by reducing ubiquitination of NKCC1 (a posttranslational change in NKCC1). They concluded that having a biomedical procedure for controlling NKCC1 protein expression opens the doors for therapeutic interventions for diseases involving the mis-regulation or depletion of NKCC1 proteins, for example during aging in the cochlea.

Based on these provocative cell line studies, Frisina et al. (2016) then conducted multidisciplinary experiments to test ALD's possible therapeutic effects in vivo. To accomplish this, they treated middle age CBA/CaJ mice with ALD for 4 months. Serum measurements of ALD levels confirmed that at the end of the treatment period, ALD blood concentrations in the aging mice had been restored to the normal, young adult range, and the mice had normal blood pressures. They found that hearing thresholds (ABR audiograms), and suprathreshold physiological responses, *significantly improved* in the ALD-treated mice compared to the non-treatment control group (saline) (Figs. 12.2 and 12.3). In terms of cellular and molecular mechanisms underlying this therapeutic effect, additional experiments revealed that SGN survival was significantly improved (Fig. 12.4), cochlear MCRs were upregulated via post-translational protein modifications (Fig. 12.5), and age-related intrinsic and extrinsic apoptotic pathways were blocked by the ALD therapy.

The functional hearing benefits of the ALD treatments in these mice were measured with behavioral methodologies (Halonen et al. 2016). Prepulse inhibition (PPI) of the acoustic startle response (ASR) was employed as the functional measure of auditory processing, with a 4-month repeated measures experimental paradigm. The 4-month, long-term treatment with ALD improved the behavioral measures of hearing, with the PPI of the ASR data displayed in Fig. 12.6. Lastly, during this treatment period, they also observed that the animals' blood pressures remained normal, indicating that the ALD was not at abnormally high levels. Taken together with the Ding et al. and Frisina et al. findings presented earlier in this section, this multidisciplinary body of results is the first to demonstrate protective effects of ALD for ARHL. It paves the way for translational drug development, using ALD as a key component to prevent or slow down the progression of ARHL.

12.2.1.4 Hormonal Interventions: Is Hormone Replacement Therapy the Answer?

Guimaraes et al. (2006) undertook the largest clinical investigation of the effects of hormone replacement therapy (HRT) on ARHL. They analyzed and compared hearing test results for 124 postmenopausal women taking HRT, who were treated with the most common form of HRT used clinically, the combination of estrogen and

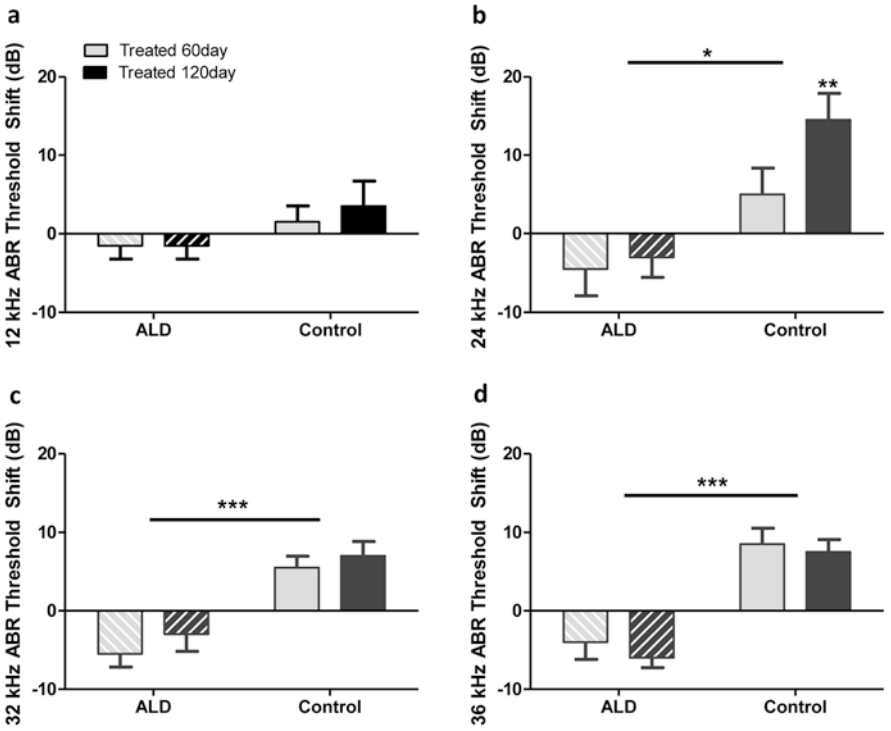

Fig. 12.2 Auditory brainstem response (ABR) threshold shifts (dB) for treated and untreated (control) subject groups following 60 and 120 days of treatment. 12 kHz (**a**), 24 kHz (**b**), 32 kHz (**c**), and 36 kHz (**d**). Mean (± SEM) frequency-specific ABR threshold shifts in the treatment group ($N = 5$) on days 60 and 120 compared to the control group ($N = 5$) values, showed improved hearing sensitivity for all four test frequencies, with the greatest benefit at the higher frequencies. "0" on the ordinate represents the baseline (pretreatment) ABR thresholds. Negative threshold shifts represent improvements in hearing with time in the aldosterone (ALD) treatment group, while positive shifts indicate age-related ABR threshold elevations in the control group. (**e**) ABR audiogram data upon which Fig. 12.1a–d are based. (Top) Very little change in auditory sensitivity occurs in the ALD treated mice. Bottom: The control mice show typical ARHL threshold elevations over the 4-month treatment period. Graphs show means (± SEM); solid line is the pretreatment baseline ABR audiogram; the dotted line is for 60 days, and the dashed line is for 120 days of treatment. ANOVA: $*p < 0.05$ for 60 days; $**p < 0.01$ for 120 days, $****p < 0.0001$ for 120 days. (From Frisina et al. 2016, without alteration, with permission according to the Creative Commons License: https://creativecommons.org/licenses/by/4.0/)

progestin (E + P; $N = 32$); or E alone ($N = 30$), to a third non-HRT ($N = 62$)] control group. The women were 60–86 years old and were matched for age and health status across the subject groups. All had relatively healthy medical histories, with no significant noise exposure, middle-ear problems, or major surgeries. Hearing tests included pure-tone audiometry (PTA); tympanometry, a test of middle ear status; DPOAEs and transient evoked otoacoustic emissions (TEOAEs), which measure the health and functionality of the cochlear outer hair cell system; and the

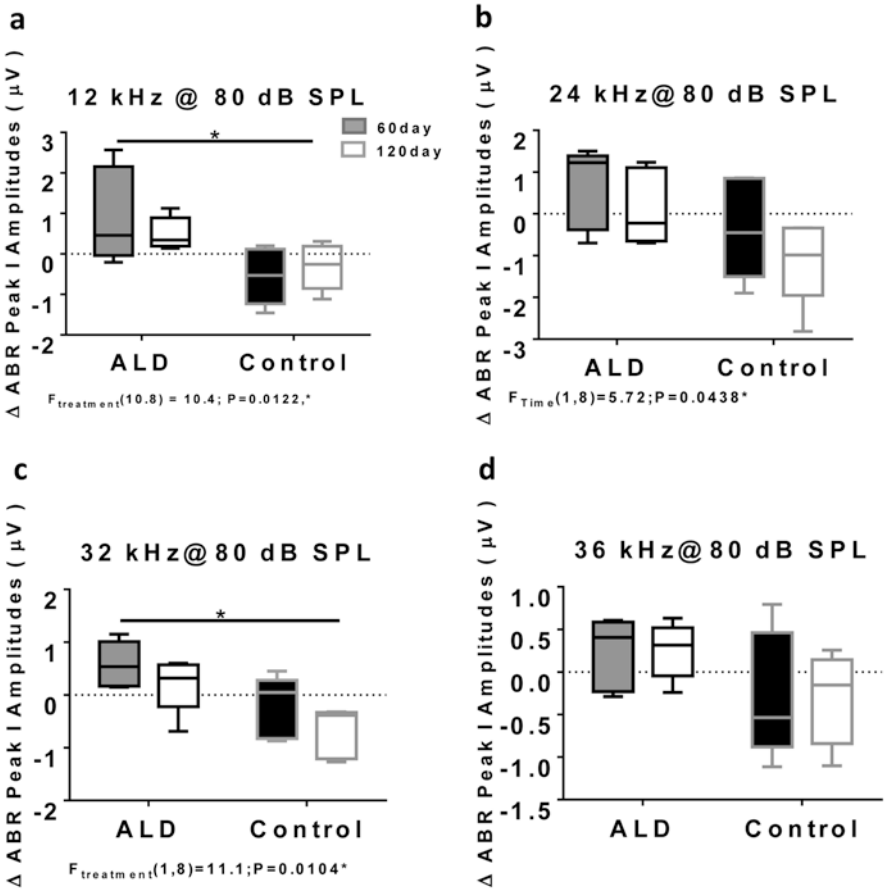

Fig. 12.3 Auditory brainstem response (ABR) peak 1 amplitude changes (μV) at 80 dB SPL, for treated and untreated (control) subject groups, following 60 and 120 days of treatment. 12 kHz (**a**), 24 kHz (**b**), 32 kHz (**c**), and 36 kHz (**d**). Box plots (median, first, and third quartiles, whiskers: minimum and maximum) of frequency-specific ABR P1 amplitude changes in the treatment group ($N = 5$) on days 60 and 120 compared to the control group ($N = 5$) values, showed improved hearing, i.e., increased ABR amplitudes, for all four test frequencies, with the greater benefits at the higher intensities. "0" on the ordinate represents the baseline (pretreatment) ABR amplitude levels. Positive shifts represent increased excitatory drive with time in the aldosterone treatment group, while negative shifts indicate age-related ABR level decreases in the control group. ANOVA: *$p < 0.05$; error bars are SEM. (From Frisina et al. 2016, without alteration, with permission according to the Creative Commons License: https://creativecommons.org/licenses/by/4.0/)

Hearing-In-Noise Test (HINT) that tests for speech perception in background noise, the number one complaint of hearing-impaired persons being that they cannot understand speech in acoustically cluttered listening environments. Pure-tone thresholds in both ears were elevated (poorer) for the E + P subjects relative to the E and control groups, as shown in Fig. 12.7. For DPOAEs, the E + P group

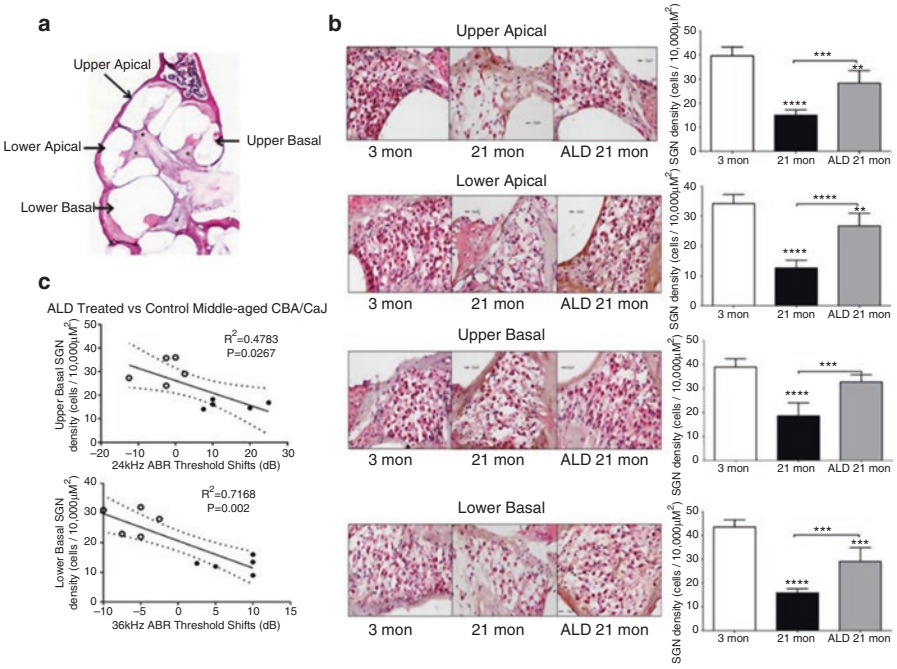

Fig. 12.4 Hematoxylin/eosin (H&E) staining patterns in the cochlea reveal SGN loss with age, and rescue with aldosterone (ALD) hormone treatments. (**a**) Cross section of the complete CBA mouse cochlea showing all turns: Section-thickness is 5 μm, Magnification: 2.5 × 1.6. All cochlear turns are distinguishable as: upper apical, upper basal, lower apical and lower basal. The cell number measurements of spiral ganglion neurons (SGNs) included all turns: (**b**) SGN cell count densities were measured by light microscopy for the young adult (left) and middle-aged mice with (right) and without (middle) ALD treatments. Magnification: 20 × 1.6. Right panels show bar graphs representing the SGN cell density. Mean ± SEM for each subject group. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, $****p < 0.0001$. (**c**) Statistically significant correlations between SGN density and 24- and 36-kHz auditory brainstem response (ABR) threshold shifts indicate that a reduction in the number of SGNs are associated with poorer hearing (higher ABR thresholds). Open points are for ALD-treated animals, and filled points are for the controls who are undergoing normal age-related hearing loss. According to the physiological place-frequency map of the mouse cochlea, 24- and 36-kHz shifts are located at upper and lower basal turns of the cochlea, which correspond to the cochlear locations with the most cell density loss with age in CBA/CaJ mice. (From Frisina et al. 2016, without alteration, with permission according to the Creative Commons License: https://creativecommons.org/licenses/by/4.0/)

presented with lower (worse) amplitude levels than the E and control groups. For the HINT, the E + P group showed poorer speech perception than the E and control groups for speech in background noise and also for speech in quiet. These clinical results indicate that the combination of E + P HRT results in poorer hearing abilities in aged women, affecting both the peripheral (inner ear) and possibly the central (brain) auditory systems; and HRT disrupts the perception of speech in background noise.

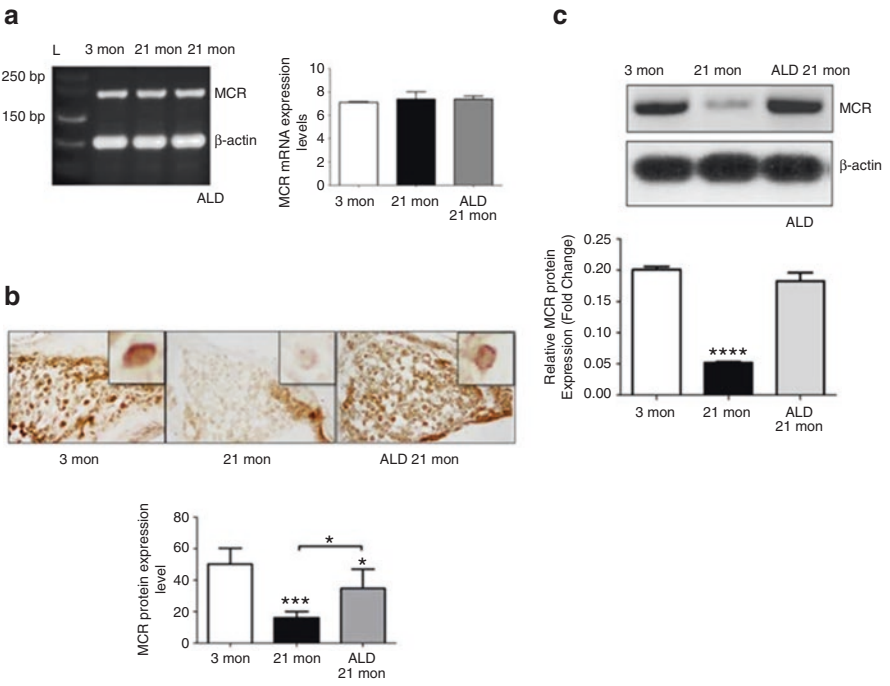

Fig. 12.5 Mineralocorticoid receptor (MCR) presence in spiral ganglion neurons (SGNs) from young adult (3 mon), and aged (21 mon) control mice and those which were treated with aldosterone (ALD) from their 17th month of age up to 21 months. (**a**) mRNA gene expression of MCRs in young adult, aged mice, and aged mice with ALD treatment were all of similar magnitudes. 3 mon: Modiolar samples from young adult mice, 21 mon: Modiolar samples from aged mice. L-Ladder: DNA molecular weight. (**b**) The MCR protein expression level was determined by densitometry analysis (MetaMorph Image Analysis System) of immunocytochemistry sections; upper panels show representative sections for the MCR antibody staining. The insets in the upper panels represent a typical MCR-DAB stained SGN. The lower panel presents a bar graph summarizing the relative densities from densitometry measurements: Mean ± SEM for each group. (**c**) MCR protein expression in SGNs shown by western blots of modiolar tissue samples. The expression level is reported relative to the expression of beta-actin as the loading control. For both measures of protein expression (**b** and **c**), the ALD treatments helped rescue the age-related declines in MCR protein expression. Statistical significance: $*p < 0.05$, $**p < 0.01$, $***p < 0.005$, $****p < 0.001$. (From Frisina et al. 2016, without alteration, with permission according to the Creative Commons License: https://creativecommons.org/licenses/by/4.0/)

Follow-up studies in mouse animal models of presbycusis confirmed the main findings of the clinical study. In particular, Price et al. (2009) mimicked key aspects of the clinical investigation, by giving HRT to aging, perimenopausal female CBA/CaJ mice via subcutaneous, time-release pellets. This experiment used the same three subject groups as the human study: E + P (combination HRT), E, and saline control. ABRs (sensitivity of the auditory system) and DPOAEs (cochlear outer hair cell system health and functionality) were employed. Longitudinal comparisons of ABR threshold data obtained over a 4-month treatment duration revealed

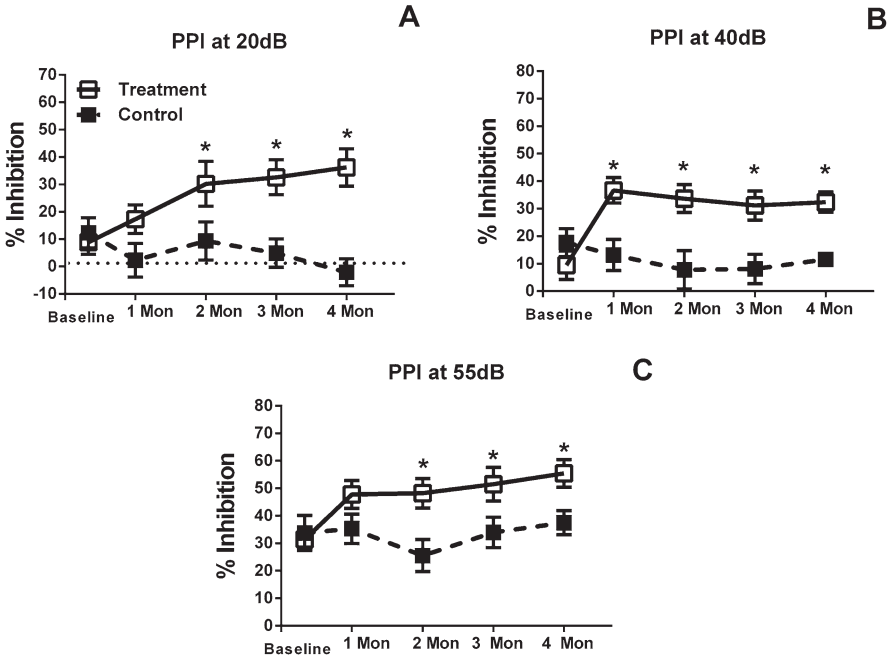

Fig. 12.6 Noise burst prepulse inhibition (PPI) at various prepulse intensities for treated (open squares) and untreated or control (filled squares) mice across the 4-month period. Inhibition levels for a 20 dB prepulse (**a**), the 40-dB prepulse (**b**), and 55-dB prepulse (**c**). Significant increases in inhibition emerged in the treated group at the 2-month testing point and continued throughout testing. A similar pattern was seen for the 55-dB prepulse shown in **c**, with expected overall inhibition increases due to the increasing prepulse intensity. Significant differences in mean % PPI are indicated by the (*). (From Halonen et al. 2016, with permission)

statistically significant declines in auditory sensitivity over time for the E + P treatment group. The E only mice revealed milder changes at 3-, 6-, and 32-kHz. DPOAE testing revealed statistically significant differences for the E + P combo treatment group in the high and middle frequency ranges (15–29 and 30–45 kHz) after as early as 2 months of treatment. Statistically significant poorer DPOAEs (lower amplitudes) were also seen at four months of treatment across all frequencies for the combined HRT group. These data confirm the main human clinical findings: HRT therapy impairs OHC functioning and overall auditory sensitivity. These findings further indicate that E + P HRT may actually accelerate ARHL, relative to E monotherapy; findings that are consistent with the clinical hearing loss observed in aging women who have taken combination HRT.

In summary, it may be that E alone has some clinical applicability for preventing or treating some key aspects of ARHL (Williamson et al. 2019); however, systemic side effects such as increased chance for ovarian, breast or uterine cancer, or other age-linked medical conditions related to elevated E levels during aging, may prohibit this approach. Utilizing local delivery of E to the inner ear may obviate these

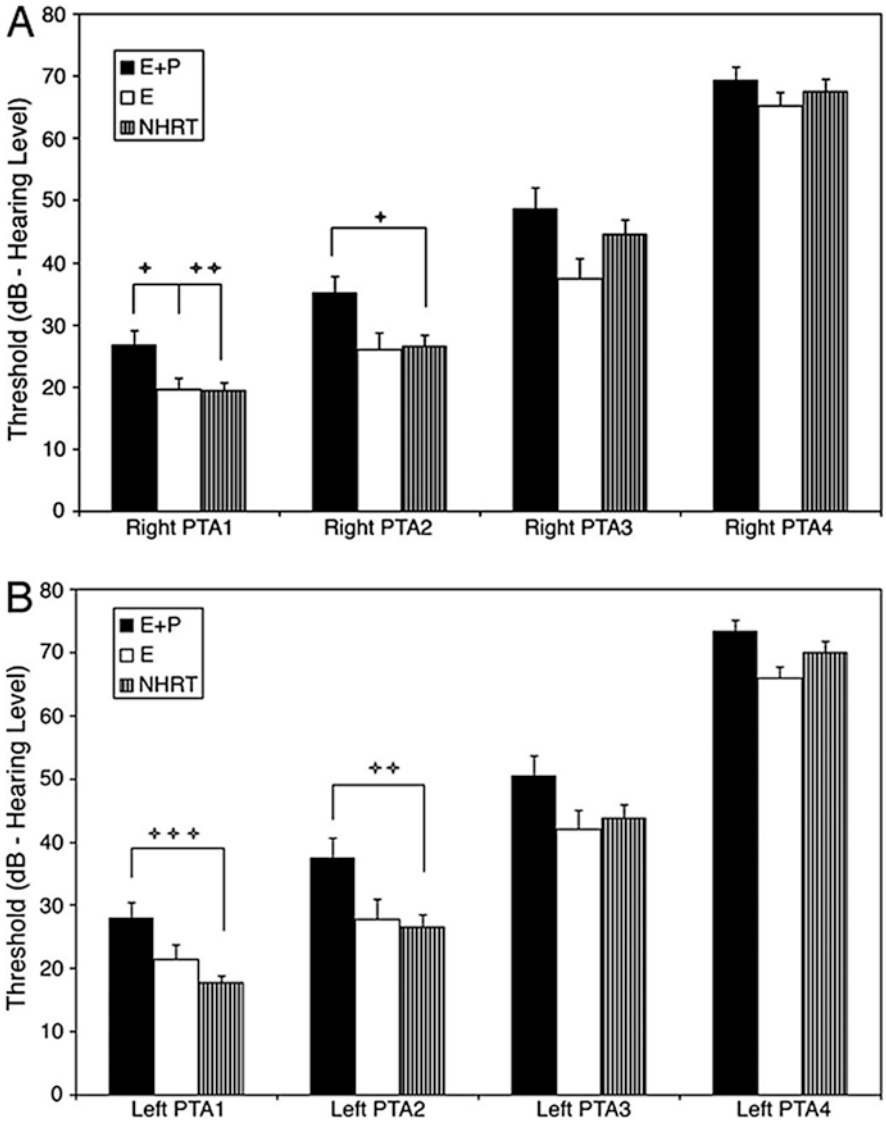

Fig. 12.7 Comparisons between estrogen plus progestin (E + P), estrogen E, and the control group, which did not receive hormone replacement therapy (HRT, NHRT), for pure-tone thresholds in the right ear (**a**) and left ear (**b**). The E + P group presented with elevated thresholds relative to the E and the NHRT groups at all frequencies, with statistically significant differences for both ears for PTA1 and PTA2. PTA1 represents the average of thresholds for frequencies 0.5, 1, and 2 kHz; PTA2 for 1, 2, and 4 kHz; PTA3 for 4, 8, and 9 kHz; and PTA4 for 10, 11.2, 12.5, and 14 kHz. PTA, pure-tone average. +p0.05; ++ p0.01; +++p < 0.001. (From Guimaraes et al. 2006, with permission)

side effects and provide safe and efficacious clinical outcomes. Some of these local drug delivery approaches are presented in Sect. 12.2.3, including hydrogels and micropumps.

12.2.1.5 The First Phase 2 FDA Clinical Trial for Age-Related Hearing Loss

Voltage-gated potassium (Kv) channels comprise a group of important membrane ion channels critical for nerve cell functioning. These channels have different structural and functional variations, with Kv1.1 and Kv3.1 being present in neurons of the auditory system (Grigg et al. 2000).

One of the hallmarks of ARHL is that even older listeners with normal or relatively favorable audiograms, when tested with complex sounds such as speech-in-noise stimuli, perform more poorly than young adults with normal hearing (e.g., Fitzgibbons and Gordon-Salant 1994; Frisina and Frisina 1997). This finding could result from aging of the brain, and specifically neural processing deficits in the brainstem and cortical auditory systems (Walton et al. 1998). One of the cellular bases of these age changes is likely the age-related declines in the expression, and therefore functionality, of Kv channels in brainstem auditory neurons (Zettel et al. 2007).

The Kv3.1 channel, a member of the *Shaw* Kv family, has a relatively high activation threshold, about −10 mV, and rapid activation and deactivation kinetics consistent with a delayed rectifier (Kanemasa et al. 1995; Li et al. 2001). Previous investigations indicate high expression levels in the normal, young adult auditory brainstem, particularly in the medial nucleus of the trapezoid body (MNTB) and other parts of the superior olivary complex (SOC) such as many of the periolivary nuclei, including those containing cell bodies of the medial olivocochlear (MOC) efferent system. Kv3.1 is also located in the bushy cells for the anteroventral cochlear nucleus (AVCN), another auditory brainstem neural circuit component involved in sound temporal coding. Functionally, the Kv3.1b channel protein is critical for the rapid repolarization of the action potential required for quick activation and deactivation ion channel activity needed for accurate temporal processing (Wang et al. 1998; Brew and Forsythe 2005). Pharmacological, computational, or genetic removal of Kv3.1 cellular currents in neurons broadens the action potential width and makes neurons unable to follow rapid stimulus patterns and pulse trains (Kaczmarek and Zhang 2017). In addition, evidence suggests that the MOC efferent system is an auditory brainstem neural circuit that plays a role in enhancing signal processing in background noise and improving auditory selective attention (Puel et al. 1988). As aging mice and humans have difficulty with these tasks (Willott 1990; Snell and Frisina 2000), it is likely that the Kv3 channel alterations are a potential cellular mechanism for age-linked declines in speech and temporal processing, involving neurons at the level of the SOC, such as the MOC efferent system neurons.

To examine this notion Zettel et al. (2007) explored the expression changes of Kv3 channels in the auditory brainstem with age and also tested the functional effects on hearing for Kv3.1 knockout mice. Specifically, Kv3.1 mice were divided into 3 groups of $N = 12$, including (knockout, −/−), (heterozygotes, +/−), and (wild type, +/+). ABRs, DPOAEs, and contralateral suppression (CS) of DPOAEs were obtained for young adults (age 1–2 months). As presented in Fig. 12.8, they found that the absolute amount of CS, an indicator of the strength and health of the MOC efferent system, was greatest in the wild types, intermediate in the heterozygotes (+/−), and the least present in the homozygote knockouts. Additionally, immunocytochemical results indicated that Kv3.1 channels decline with age, starting in middle age, which is correlated with the time course of CS decline (Zhu et al. 2007). Zettel et al. also observed evidence for decreased size of MOC neuronal cell bodies in older animals. Together, this body of evidence indicates that Kv3.1 channels make up one of the key biological bases of central auditory ARHL. In sum, declines in the MOC efferent system (CS of DPOAEs) result in declines in OHC function (DPOAEs), which result in poorer (elevated) hearing thresholds. Age-linked alterations in Kv3.1 may spark MOC efferent system declines, leading to the above progression of events.

Autifony Inc., a drug R&D company based in the United Kingdom, developed a drug to modulate voltage-gated potassium channels in the auditory brainstem, based on the prior studies summarized earlier in this section, which showed that these

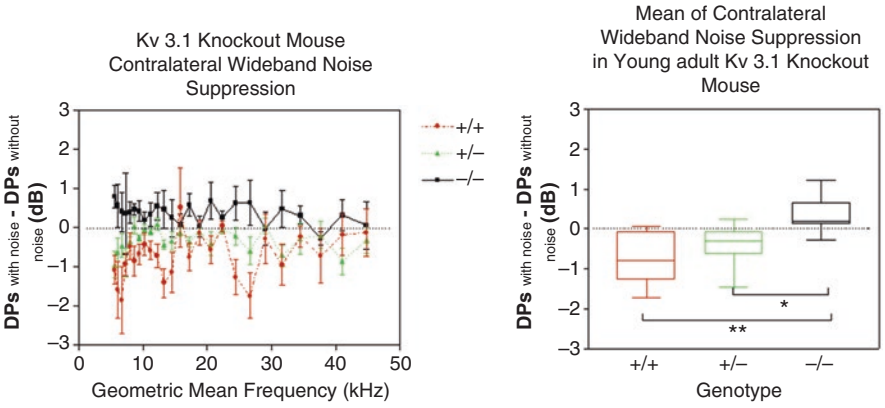

Fig. 12.8 Comparison of auditory function in Kv3.1b (knockouts, black), +/+ (wild type, red), and +/− (heterozygote, green) mice at 6–11 weeks of age. (Left) The knockout mice have no measurable contralateral suppression (CS), so no medial olivocochlear (MOC) efferent feedback activity and are significantly different from wild-type mice at many frequencies above, and at all frequencies below, 16 kHz. (Right) Box plots (median, interquartile ranges, and total range) summarizing contralateral suppression–distortion-product otoacoustic emissions (CS-DPOAEs, a quantitative measure of the strength of response of the auditory efferent feedback system) of the three genotypes. There was a statistically significant difference between the knockout mice compared to both +/− and +/+ mice. The *y*-axis is a quantitative measure of the strength of the MOC efferent feedback system (DP amplitude in the presence of the contralateral noise − DP amplitude in quiet). (Adapted from Zettel et al. 2007, with permission)

channels decline with age and are involved in auditory temporal and efferent system processing at the brainstem level. Specifically, their drug (AUT00063) modulates the physiological activity of Kv3.1 and Kv3.2 by enhancing Kv conductances by shifting the voltage dependence of activation of the channels to more negative potentials (Brown et al. 2016).

Autifony's research program demonstrated that AUT00063 improved auditory temporal processing in aged animals (Chambers et al. 2017). Their in vivo experiments induced a selective, near-complete elimination of auditory nerve fiber activity in mice, which in some ways simulates the age-linked decline in the outputs of the cochlea characteristic of ARHL. Chambers et al. observed normal DPOAE thresholds for deafened and untreated ears of their mice, indicating normal OHC functionality in the deafened cochleae. Using in situ hybridization techniques, they discovered that similar to the MOC neurons (Zettel et al. 2007), there are significant expression levels of Kv3.1 in IC and auditory cortical neurons, as presented in Fig. 12.9. Subsequent neural recordings in the central auditory system of the deafened mice indicated that temporal processing deficits existed that could not be

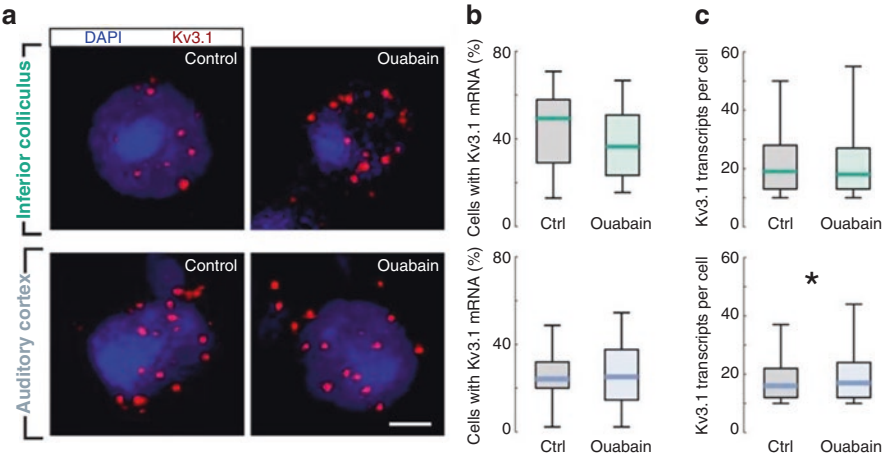

Fig. 12.9 Kv3.1 mRNA is expressed in the inferior colliculus (IC) and auditory cortex (ACtx), even after profound contralateral auditory nerve damage. (Top row) IC. (Bottom row) Auditory cortex. (**a**) Individual KCNC1 mRNA transcripts that encode the Kv3.1 protein identified near DAPI-labeled nuclei of individual cells. Fluorescently labeled individual mRNA transcripts are identified within a fixed radius of each nucleus, counted, and then assigned to a given cell with automated software. Scale bars = 3 μm. (**b**) The percentage of DAPI + nuclei within a 185 μm^2 region of interest that contain at least 10 mRNA transcripts are quantified in the ICc (top) or ACtx (bottom) 30 days after control or ouabain treatment (N = 36 imaging regions from 4 ouabain-treated mice and 27 imaging regions from 3 sham-treated mice). (**c**) Same as **b**, except the number of identified transcripts are quantified only in the Kv3.1 + cells (N = 2420/2814 in the ICc and 941/1399 cells in ACtx for control/ouabain, respectively). Plots in **B** and **C** depict the median, interquartile range and 95% confidence intervals. Asterisk indicates $p < 0.05$ with a rank sum test; otherwise, pairwise differences between control (Ctrl) and ouabain are not significant. (From Chambers et al. 2017, without alteration, with permission according to the Creative Commons License: https://creativecommons.org/licenses/by/4.0/)

explained by sensitivity (threshold) differences. Indeed, in auditory cortex where temporal coding is poor under certain conditions, AUT00063 significantly boosted temporal decoding accuracy, particularly at fine temporal resolutions.

Autifony conducted an FDA Phase 1, double-blind, randomized, crossover, single escalating dose clinical trial in healthy young (18- to 45-year-old) men, which indicated safety of AUT00063. The trial was extended to include subjects over the age of 60 (men and women), with excellent pharmacokinetics when given on a daily basis. This drug has effects for a number of hours, so the dosing regimen involved giving the drug each day to improve complex sound processing; much in the same way persons with attention deficit disorder (ADD) take Ritalin each morning to improve their abilities to focus and concentrate during the day. Unfortunately, although there were some interesting trends in the data of this pioneering FDA Phase 2 clinical trial, this drug did not show any significant sound processing improvement effects. Species or dosage differences might account for this lack of effectiveness of AUT00063 in aging humans.

12.2.2 Technological Advances for New Therapeutic Compound Delivery to the Cochlea

If targeted, local cochlea drug delivery was feasible clinically, it would open up a whole new set of options for delivering efficacious drugs, including those with systemic side effects. Indeed, exciting new possibilities for chronic, local drug application to the cochlea are emerging, i.e., hydrogels in conjunction with transtympanic injections, and micropumps for inner ear drug delivery. El Kechai et al. (2015) provide an enlightening summary of some of the relative advantages, disadvantages, and strategies for cochlear drug delivery options versus systemic therapeutic compound delivery; see Fig. 12.10. These possibilities for local drug delivery over extended periods allow for the use of a much broader range of FDA-approved drugs, because systemic side effects are avoided, and much more precise control of drug delivery and intracochlear concentrations can be achieved with higher levels of precision than oral or injection whole-body techniques.

An additional consideration is that a biomedical therapy to slow down or prevent salient features of presbycusis will need to be applied over a somewhat long period of time, to minimize any side effects by using lower dosages (if a systemic delivery is used), and achieve therapeutic success. The same might be true for preventing noise-induced hearing loss for persons who work each day in noisy environments, but because of the nature of their profession and duties, cannot achieve full hearing protection with ear plugs or other types of hearing protector systems. As a better option, a different, more temporally sustained approach is needed for ARHL or long-term noise exposures, versus applying a medicine or drug to prevent an acute noise exposure or prevent hearing loss due to short-term use of an ototoxic antibiotic or chemotherapeutic agent.

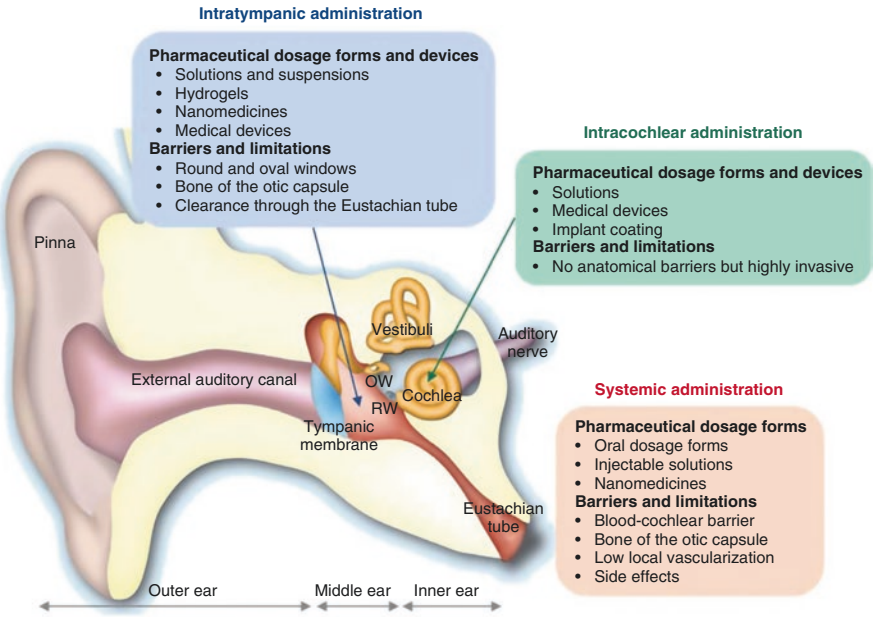

Fig. 12.10 Diagram showing the target areas for intracochlear, extracochlear, and systemic drug delivery into the inner ear. (From El Kechai et al. 2015, with permission)

12.2.2.1 Programmable Micropumps for Cochlear Drug Delivery

Some laboratory animal-size micropumps are currently under development or on the market, such as the iPRECIO SMP-300 developed by Alzet. It is relatively small, 24.8 × 15.0 × 7.2 mm, so can be used in smaller rodents, such as rats or guinea pigs subcutaneously, but although marketed for mice, it is still a bit large for chronic implantation that would be needed for preventing or treating ARHL. It has some innovative features, such as a useful reservoir volume of 130 μl, a good flow rate range of 0.0–10 μl /hr (0.1 μl /hr resolution), biocompatibility, and preprogrammed programmability via wireless communication. In vivo reprogramming is not currently available.

Borenstein and colleagues have made great progress on development of microfabricated mini-pumps for inner ear drug delivery based upon a reciprocating infusion paradigm and electronically controlled dosing (Leary-Pararas et al. 2012; Tandon et al. 2016). By integrating a drug reservoir and all the fluidic components into the microfluidic structure of the pump, they realized a drug delivery system that is more robust and leak-proof compared to previous systems that employed separate, tubing-connected components prone to leakage. The advantage of the reciprocating system design is that for cochlear infusions, it minimizes the addition of fluid to the inner ear via the cochleostomy, reduces fluid pressure changes, yet can deliver a drug or therapeutic agent effectively. Borenstein's group has demonstrated infusion success and precision with their pumps. Currently their pumps are too large for

subcutaneous implantation, being several centimeters in terms of length and width, but they can be worn as a backpack or head mounted on the larger rodents such as guinea pigs (Borenstein 2011).

Given the advantages of the wide array of transgenic animals, the mouse is a desirable animal model, but designing pumps for such small animals is very challenging. The mouse cochlea's volume is less than 1 μl, so infusion rates have to be on the order of dozens of nl/min, and even a small leak in the microfluidic infusion system can disrupt calibrated infusion rates and volumes. Studies have worked out reliable infusion paradigms, utilizing both salicylate drug delivery to the mouse cochlea to reversibly reduce DPOAEs and delivery of contrast agents (such as the iodine-based fluid Isovue) for the first noninvasive, micro-CT images of contrast agent infused in real-time into the mouse cochlea (Borkholder et al. 2010, 2014). A mouse study has also reported on quantitative spatiotemporal modeling of the fluid and solute flow based on the micro-CT scans obtained during middle ear applications and cochleostomy infusions (Haghpanahi et al. 2013). To increase measurement accuracy, this group performed a subject-atlas image registration to exploit the information readily available in the mouse atlas images and passed segmentation or labeling information from the atlas to μCT scans. This approach had the capability to quantify concentrations at any point along the fluid-filled scalae of the inner ear, allowing for determination of spatially dependent diffusion and clearance parameters for enhanced models. Borkholder and Frisina's group is currently developing fully implantable, programmable micropumps with the same precise infusion capabilities (Forouzandeh et al. 2019).

12.2.2.2 Injectable Hydrogels for Inner Ear Applications

In general, the research on biologically implantable hydrogel drug carriers is quite extensive, and a comprehensive treatment goes beyond the scope of the present exposition (Li and Mooney 2016). Major theoretical advantages of current hydrogels and those in development are that they can deliver a variety of drugs and therapeutic compounds to a localized region of the body, such as the middle or inner ear, and they can degrade over time in a biocompatible way (no side effects), so removing them at a future time with an additional medical or surgical procedure is not necessary. An additional plus for the application of hydrogels in auditory work is that systemic drugs have difficulties transferring through the blood–labyrinth barrier, and there is somewhat limited blood flow volume to the cochlea. For example, some clinically accepted treatment options for sudden sensorineural hearing loss involve the systemic delivery of corticosteroids, which often leads to significant improvements in hearing but, owing to the high dosages, carries side effects such as inhibiting adrenal response, osteoporosis, hyperglycemia, hypertension, and osteonecrosis (Spear and Schwartz 2011). Although this interdisciplinary field of hydrogel development has not yet progressed to the point of treating ARHL, two examples of hydrogel applications for treating hearing loss will be presented here, to give a

flavor of how this field involves the intersection of materials science, biomedical engineering, neuro-otology, and hearing research.

Perhaps the most investigated area so far is the use of hydrogels to improve the implantation, cochlear cell survival and hearing measures for cochlear implants. For instance, it has been shown in animal models that these types of applications can improve certain cochlear implant outcomes. Hütten et al. (2014) followed up on the observations that fibrous tissue growth/immune response and loss of residual hearing after cochlear implantation can be reduced by treatment with the glucocorticoid dexamethasone-21-phosphate-disodium salt (DEX) but so far there is no clinically approved procedure for delivering this to cochlear implant patients. So, Hutten et al. (2014) developed a new way of continuous local drug delivery to the cochlea using a refillable hydrogel functionalized silicone reservoir. A polyethylene glycol–based hydrogel made of reactive NCO-sP(EO-stat-PO) prepolymers was invented for both in vitro and in vivo use. Encapsulating the free form hydrogel into a silicone tube with a tiny port for the drug diffusion enabled delayed drug release. Also, controlled DEX release over several weeks was achieved using the hydrogel filled reservoir. Utilizing a guinea pig cochlear trauma model, the reservoir delivery of DEX significantly protected residual hearing and reduced fibrosis. Hutten et al. concluded that their inner ear hydrogel system could be used in its own right or in combination with cochlear implants to provide sustained drug therapies to the inner ear. Similar approaches are being successfully pursued by other groups as well in guinea pig and alternative animal models, such as work being done by Honeder et al. (2016) and Plontke et al. (2017).

Hydrogel delivery to the middle ear and/or round window has also been used in rodents to attenuate acute hearing loss insults such as noise-induced or drug-induced hearing impairment. For instance, as proof-of-concept, Lee et al. (2007) administered insulin growth factor-1 (IGF-1) to guinea pigs via hydrogel placed on the round window membrane. Their findings showed that animals that had their IGF-1 hydrogels implanted shortly after noise exposure had significantly lower hearing thresholds than control animals, most notably at 4 and 8 kHz. Also, the cochlear inner and outer hair cells were significantly more intact for the IGF-1–treated animals after noise exposure. It should be noted that this is one of the few studies to have attenuated the effects of noise-induced hearing loss utilizing middle ear drug applications, in this case utilizing a hydrogel.

12.2.2.3 Acoustic Approaches: Sound Supplementation Strategies

As an alternative to drug/medication approaches to curtailing ARHL, previous preclinical research by Willott, Turner, Walton, and others (summarized in the text that follows) has yielded interesting possibilities for the idea of presenting sounds to aging animals to slow down the progression of ARHL. New hearing aid technologies where the hearing instruments can produce a variety of sounds, as well as amplify them, allows for an audiological clinical technique for delivering therapeutic acoustic stimulation at certain times, durations, and sound spectra. This special

acoustic stimulation is sometimes referred to as an augmented acoustic environment (AAE).

Of course, how much sound supplementation, the nature of the sounds, and what durations and levels are most beneficial, while not harmful, have yet to be determined for treating ARHL, but are being investigated by research audiologists and hearing scientists (Bielefeld et al. 2010). The initial excitement in this area for possible ARHL interventions was generated when Willott and Turner employed mouse ARHL animal models. They exposed aging mice to different types of ongoing sounds in their living environments (Turner and Willott 1998). Using different strains of mice, which lose their hearing at different rates with age, they uncovered some positive effects of long-term supplemental sound stimulation. For example, they utilized DBA/2 J (DBA) mice, which develop a high-frequency hearing impairment starting around the time of weaning/puberty (3–4 weeks old) that becomes severe by 3 months of age. Mice were exposed 12 hours per night for 10 nights to a 70 dB SPL broad-band noise AAE starting at one of three ages, ranging from the onset of hearing loss (about 30 days old) to when hearing loss was more severe (40 days and 50 days old); control animals did not receive the AAE. C57BL/6 J (C57) mice of the same ages provided a comparison group of mice that were age-matched, for both the exposed and unexposed/control conditions. The ABR, ASR amplitude, and PPI were used to measure hearing capabilities throughout the experiments. The AAE had significant effects on DBA mice, but had no effect on C57 mice, which had normal hearing sensitivity during this study. For the most part, AAE exposure resulted in improved auditory performance in DBA mice (better PPI, lower ABR thresholds, and greater ASR amplitudes). However, mouse age and/or degree of hearing loss proved to be a key parameter. For example, improvement of PPI took place only when the AAE was initiated later in the course of hearing loss (35 days of age or older); in contrast to this, beneficial effects on ABR thresholds were observed only when the AAE was started early in the course of hearing loss (<45 days old).

A series of additional investigations by Willott and Turner's groups revealed more provocative characteristics of some of the beneficial effects to the auditory system of the AAEs, in terms of hearing abilities and the underlying cellular mechanisms and anatomical changes that subserve these beneficial effects. For instance, Willott et al. (2005) reported that at 55 days of age, AAE-exposed animals showed less elevation of ABR thresholds, fewer missing hair cells, and greatly reduced loss of AVCN volume and neuron number compared to untreated control mice (see Fig. 12.11). They hypothesized that the central neuroprotective effect in the CN was linked to the increased afferent input to the CN neurons caused by the AAE, which induced a healthier cochlea and boosted its outputs to the CN via the auditory nerve fibers of the eighth cranial nerve.

Since Willott and Turner's pioneering studies in mouse animal models of ARHL, progress has been made in this exciting area, including clinical studies in human listeners. In particular, there is considerable evidence that, over time, chronically

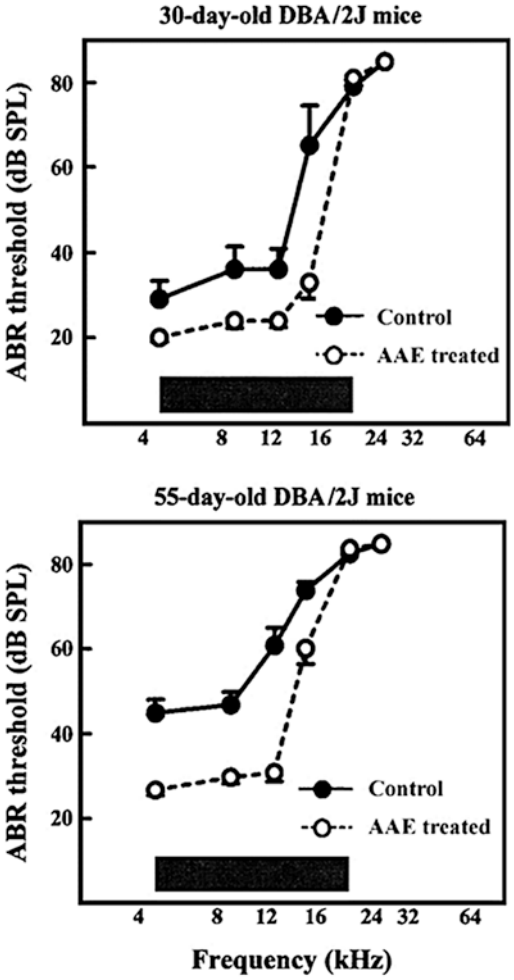

Fig. 12.11 Auditory brainstem response (ABR) thresholds of young DBA/2 J mice (means ± SEMs). Mice were tested at 30 days of age (top) and 55 days of age (bottom). Augmented acoustic environment (AAE)-treated mice (open circles) were treated nightly with the AAE beginning before 12 days of age. The cross-hatched bar approximates the effective frequency spectrum of the AAE noise band (see text). AAE-treated mice had lower thresholds at tested frequencies below 24 kHz. Note that ABRs could not be obtained for 32-kHz tones and higher because of basal cochlear damage; 85 dB "thresholds" are shown for graphic perspective with respect to the frequency representation of the normal mouse cochlea (i.e., the 32–64-kHz points were not obtained from ABRs). (From Willott et al. 2005, with permission)

altered hearing via hearing aid amplification can lead to acclimatization that includes changes in loudness growth, loudness tolerance, preferred loudness levels, and performance on tasks that involve loudness perception such as intensity discrimination (Munro 2008; Munro and Merrett 2013). Similarly, numerous studies have shown that the prolonged use of ear-level sound generators (sound supplementation) or the use of ear plugs (auditory deprivation) lead to changes in loudness tolerance and growth (Formby et al. 2002, 2003, 2007) and acoustic reflex thresholds (Munro and Blount 2009), with both of these peripheral stimulation conditions altering the balance of excitation and inhibition in the central auditory system over time.

12.3 Ear and Brain Training Techniques

There is a clinical research literature emerging on possibilities for regular acoustic training sessions as a means of retarding the progression of key features of ARHL, i.e., "use it or lose it" (Chisolm et al. 2003; Chisolm and Arnold 2012). Some of these approaches are resource intensive (time, dollars), only work with persons with certain audiological profiles, and their lasting effects are still controversial. Indeed, for the most part the training effects end after the training period stops, but there are some tantalizing initial results with aging listeners, as carried out by Sweetow and Humes (Burk and Humes 2008; Humes et al. 2009, and presented in more detail by Humes, Pichora-Fuller, and Hickson, Chap. 11).

Sweetow conducted an extensive study using the Listening and Communication Enhancement (LACE™) system that his group developed to improve hearing in aging adults (Sweetow and Sabes 2006). They utilized their home-based, interactive adaptive LACE™ program that engages hearing-impaired listeners in the hearing aid acclimation process; teaches listening strategies; and purportedly builds confidence, addressing cognitive changes characteristic of ARHL. They studied outcomes using a between-group, within-subject experimental design. Their findings showed statistically significant improvements for the trained subjects on all but one of the outcome measures. However, using LACE™, Saunders, Smith, McArdle, and Chisolm did an extensive, multi-site evaluation study and showed that there was no beneficial effect of LACE™ for those subjects receiving the LACE™ training, because, unlike Sweetow and Sabes, they compared the same speech and auditory outcomes measured on control groups who received standard-of-care hearing aid intervention alone (Saunders et al. 2016).

It is also very interesting to note that there are changes in the central auditory neurophysiological mechanisms that underlie some of the speech perceptual improvements that occur during auditory training in older adults; see for example the body of work of Tremblay and colleagues (Tremblay et al. 2001, 2009; and other studies covered by Harris, Chap. 6). Typically, these improvements do not last, and often do not generalize well to speech perception situations not included in the training paradigms. It may end up being the case that benefits from "auditory exercises," like muscular exercising, persist only as long as you are on an active exercise program, and for the particular muscle systems you are exercising.

12.4 Summary

This chapter conveys much of the current excitement regarding these questions: Are the progression and symptoms of presbycusis inevitable, as communicated to patients by current audiological and otolaryngological clinical practitioners? Or can we prevent or treat ARHL? The updates and evidence presented in this chapter strongly suggest an enthusiastically positive response to the latter question, and new

possibilities in this arena are being investigated and uncovered at an accelerating rate from diverse fields such as audiology, speech sciences, hearing research, neuroscience, and biomedical engineering.

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Compliance with Ethics Requirements Dr. Robert Frisina has been awarded a patent regarding the use of aldosterone as a therapeutic compound to prevent or treat age-related hearing loss; and he filed a patent, patent under review, on a new micropump for inner ear drug delivery. Patent Rights assigned to the University of South Florida.

Carlos Cruz has no conflicts of interest.

Dr. Tanika Williamson has no conflicts of interest.

Xiaoxia Zhu, MD, has been awarded a patent regarding the use of aldosterone as a therapeutic compound to prevent or treat age-related hearing loss. Patent Rights assigned to the University of South Florida.

Bo Ding, MD, has been awarded a patent regarding the use of aldosterone as a therapeutic compound to prevent or treat age-related hearing loss. Patent Rights assigned to the University of South Florida.

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