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# Changes in the peripheral and central auditory performance in the elderly—A cross-sectional study

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## Abstract

Age-related hearing loss (ARHL, formerly presbycusis) is due to a variety of lifetime damages to the auditory system and is characterized by bilateral sensorineural hearing loss, impaired speech understanding in noise and central sound processing deficits. Despite its commonness, the pathogenesis has not been completely clarified yet; especially the existence of an independent central ARHL component still remains controversial. We present the results of a cross-sectional topodiagnostic test battery study which aimed at separating aging- and hearing loss-related effects on all parts of the auditory system by current test procedures. Three groups of 30 participants each underwent extensive topodiagnostic test procedures (otoscopy, tympanometry, questionnaires, pure-tone audiometry, DPOAE threshold measurements, auditory brainstem response, central auditory discrimination tests, and speech-in-noise test). By comparing the results of the normally hearing young (18–26 years) and healthy control group, the normally hearing elderly group (60–80 years) and the hearing-impaired elderly group (60–80 years), we deduced aging and hearing loss-related effects on auditory performance. All measurements indicated a significant deterioration of auditory performance in the elderly, partly associated with aging and partly with age-related hearing loss. Our study thereby contributes to a multifocal concept of ARHL. All parts of the auditory system are impaired by aging, age-related hearing loss, or a combination of both. Further evidence for an independent central ARHL component, not attributable to peripheral hearing loss, is provided by the results of the central auditory discrimination test.

**KEYWORDS**
age-related hearing loss (ARHL), auditory brainstem response (ABR), central presbycusis, central auditory discrimination, otoacoustic emissions

**Abbreviations:** ABR, auditory brainstem response; ANOCOVA, analysis of covariance; ANOVA, analysis of variance; ARHL, age-related hearing loss; CADP, central auditory discrimination performance; DPOAE, distortion product otoacoustic emissions; e.g., for example; FGF, fibroblast growth factor; GABA, gamma-aminobutyric acid; HC, healthy controls; HHIE(-S), Hearing Handicap Inventory for the Elderly (−Screening version); HIE, hearing-impaired elderly; ILD, interaural level difference; IPL, interpeak latency; ITD, interaural time difference; JND, just noticeable difference; NHE, normally hearing elderly; NHE15dB, NHE subgroup with PTA-thresholds below 15 dB HL at 1, 2 and 4 kHz; OHC, outer hair cell; OLSA, oldenburger Satztest, Oldenburg Sentence Test; PTA, pure-tone audiometry; PTA500-4000Hz, average PTA-threshold of both ears at .5, 1, 2 and 4 kHz; SD, standard deviation; SNR, signal-to-noise ratio; SRT $L_{50}$, speech reception threshold for 50% intelligibility (in the OLSA); Vs., versus; WHO, World Health Organization; Δ L/t/f, stimulus level/duration/frequency difference in the CADP test.

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## 1 | INTRODUCTION

Age-related hearing loss (ARHL, formerly presbycusis) is one of the most common chronic diseases in the elderly (Lee, 2013). It is characterized by bilateral sensorineural high-frequency hearing loss, deterioration of speech understanding, especially in noisy environment, and impaired central sound processing and thus can result in social isolation and depression. Estimated prevalence is high: in western countries, about 25% in their 70s and about 50% in their 80s suffer from relevant age-related hearing loss (Fischer et al., 2016; Roth, 2015).

Most commonly ARHL refers to all lifetime damage to the auditory system, as, in reality, it is hardly possible to separate pure age effects from lifetime risk factors like noise, medical and infectious harms as well as genetic disposition (Billings et al., 2012; Fischer et al., 2016; Gates & Mills, 2005). On the other hand, aging per se does not compulsorily lead up to an expressed hearing loss: Already in 1960 Rosen et al. observed that Sudanese tribal people had markedly less high-frequency hearing loss than American individuals at the same age and mainly attributed these findings to differences in lifestyle, especially due to noise exposure conditions (Rosen et al., 1962). From our modern point of view, genetic and epigenetic factors not evaluated by Rosen et al. could additionally explain these differences in hearing status (Lee, 2013; Tawfik et al., 2020).

Numerous findings in human and animal research have been concerned with the pathogenesis of ARHL over the last decades. In the classical concept, peripheral pathology (loss of cochlear hair cells, strial atrophy and loss of neurons in the spiral ganglion) was considered the most important pathogenetic factor in ARHL, with spiral ganglion neuron degeneration appearing to be the most important and constant component (Keithley, 2020; Nadol, 2010; Schuknecht, 1955; Schuknecht & Gacek, 1993). This approach is increasingly challenged nowadays: Recently, Wu et al. postulated that loss of cochlear hair cells is the main predicting factor for the pattern of the pure-tone audiogram and that strial atrophy and neuronal cell death in the spiral ganglion only play a minor role in the prediction of hearing thresholds (Wu et al., 2020). Spiral ganglion degeneration and cochlear synaptopathy could be an explanation for "hidden hearing loss," that means impaired speech understanding especially in noise with essentially preserved pure-tone thresholds (Kujawa & Liberman, 2015; Liberman & Kujawa, 2017; Wu et al., 2021). High-frequency hearing loss could rather be a sign of acoustic trauma than of aging itself (Wu et al., 2021). Furthermore, attention is additionally focused on central auditory processing and cognitive deficits in ARHL and morphological and metabolic changes in the central auditory nervous system (Humes et al., 2012; Profant et al., 2013, 2014, 2019; Slade et al., 2020). Notably the existence of central ARHL, that means an independent central auditory degeneration not attributable to peripheral hearing impairment, remains controversial (Gates & Mills, 2005; Humes et al., 2012; Profant et al., 2019). In the latest thorough literature review, Humes et al. (2012) concluded that there is increasing, but altogether insufficient, evidence for an isolated central ARHL.

**Significance**

Whereas the classical pathogenetic approach of age-related hearing loss (ARHL, formerly presbycusis) mainly concentrated on peripheral pathology (cochlear cell loss, strial atrophy, and loss of spiral ganglion neurons), attention has been focused on central auditory processing deficits in ARHL in recent years. Our multitest study not only confirms impairment of all peripheral and central parts of the auditory system in ARHL but provides new evidence for an independent central auditory ARHL component not attributable to peripheral deficits. This emphasizes the need for a multifocal diagnostic and therapeutic approach that encompasses central auditive assessments and rehabilitative strategies, like neuroprotective agents and auditory training.

Understanding the underlying pathogenetic mechanisms of ARHL is not only an academic matter: Therapy of ARHL is nowadays mainly limited to peripheral amplification by hearing aids, which are prone to low patient adherence, and by invasive techniques, like cochlear implants (Fischer et al., 2016; Gates & Mills, 2005). Because of high prices and lack of health insurance many individuals cannot afford hearing aids in the United States and Europe, leading up to high socioeconomic costs, for example due to loss of workforce, and psychosocial isolation (Fischer et al., 2016). Preventive strategies have, until now, failed to significantly reduce ARHL incidence (Rosenhall et al., 2013). A better understanding of the pathophysiologic mechanisms seems decisive for new and better diagnostic, preventive, and rehabilitative strategies. In this context, the present cross-sectional study aimed to further clarify the pathogenesis of ARHL. Special regard was paid to an independent central ARHL component. By applying an extensive state-of-the-art topodiagnostic test battery (including a new central auditory performance test) and by dividing the prospectively examined sample in three groups, we intended to separate pure age- from other hearing loss-related effects on all parts of the auditory pathway.

## 2 | METHODS AND MATERIALS

### 2.1 | Participants

In total, 97 subjects participated in the study in the University hospital rechts der Isar of the Technical University of Munich, Germany. Of these, seven subjects not meeting the inclusion criteria or fulfilling one or more exclusion criteria (see Table 1) were not considered in the analyses. The whole sample was divided into three groups of 30 participants, dependent on age and auditory status: A group of young (18–26 years) and healthy subjects with normal auditory performance (healthy controls, HC), a group of

**TABLE 1** Inclusion and exclusion criteria for study subjects

| | Inclusion criteria | Exclusion criteria |
|---|---|---|
| Age | HC: 18–26 years<br>NHE/HIE: 60–80 years | All other ages |
| Hearing loss (PTA, binaural average of 500, 1000, 2000, 4000 Hz); PTA-configuration | HC/NHE: ≤20 dB HL<br>HIE: >25 dB HL–50 dB HL; high-frequency hearing loss only (>2,000 Hz)<br>Symmetric hearing loss | All other hearing loss averages<br>Low/middle-frequency hearing loss<br>Asymmetric hearing loss (>25 dB HL difference right vs. left ear at >1 frequency) |
| Questionnaire for auditory tests (DIN EN ISO 389-9:2009–12) | | Acute ear infection<br>Tinnitus<br>Sudden hearing loss with residual hearing impairment<br>Relevant macroscopic alterations of the auditory system (e.g., of pinna or ear canal)<br>Relevant exposure to ototoxic drugs or occupational noise |
| Otoscopy | Regular ear canal and tympanic membrane configuration | Relevant alterations in ear canal (relevant exostosis) or tympanic membrane (perforations, scarring, protrusion/retraction) |
| Tympanometry | Bell-shaped compliance curve (Maximum −100 to 0 daPa) | All other compliance curves |

elderly subjects (60–80 years) with normal hearing performance as defined below (normally hearing elderly, NHE), and a group of elderly (60–80 years) hearing impaired ARHL patients (hearing-impaired elderly, HIE). Each group consisted of 15 female and 15 male subjects. This three-groups-concept aimed at dividing between pure age effects on auditory performance (by comparison between HC and NHE) and additional effects of age-related hearing loss on auditory performance (by comparison between NHE and HIE).

Auditory status was defined according to pure-tone thresholds and slightly modified grades of hearing impairment of the World Health Organization (Mathers et al., 2000; World Health Organization, 1991): The World Health Organization (WHO) defines an average hearing loss of 0 to 25 dB HL at the audiometric pure-tone frequencies 500, 1000, 2000, and 4000 Hz in the better hearing ear as "no impairment," an average hearing loss of 26 to 40 dB HL as "slight," and an average hearing loss of 41 to 60 dB HL as "moderate" impairment. We adapted this classification to the aims of our study as follows: (1) As some of the measuring methods used in our study required binaural hearing capability, average hearing loss of both ears (not only the better one) was considered. (2) The upper average limit for normal hearing performance was set to 20 dB HL (not 25 dB HL). In our study, some elderly subjects with hearing loss between 20 and 25 dB HL already fulfilled some criteria for hearing aid indication in Germany. The 20 dB limit has already been suggested in the original WHO-classification itself (World Health Organization, 1991) and is nowadays the new recommendation based on the Global Burden of Disease Expert Group on Hearing Loss (Olusanya et al., 2019). (3) The upper average limit for the hearing-impaired elderly was set to 50 dB HL. This was necessary in order to avoid incomplete data, as otoacoustic emissions usually cannot be measured for hearing loss above 50 dB HL (Janssen & Müller, 2008). Furthermore, 50 dB HL is the new limit for moderate hearing loss by the Global Burden of Disease Expert Group on Hearing Loss (Olusanya et al., 2019). Both normally hearing subjects and ARHL patients exhibit largely symmetric pure-tone audiograms of both ears (Lenarz & Boenninghaus, 2012). Consequently, significantly asymmetric hearing performance of both ears was considered as an exclusion criterion (see Table 1 for all inclusion and exclusion criteria).

Participants were recruited by several ways: Posters in the ENT outpatient department of the University hospital rechts der Isar and near the medical lecture rooms of the Technical University of Munich informed patients and students about the study. The ENT database of the University hospital rechts der Isar was automatically scanned for patients with audiograms meeting the criteria mentioned above, who were contacted by mail. Finally, all participants of our study were encouraged to inform relatives and friends about the study. Like this a cohort representative of the average population could be gained. Measurements were taken in a soundproof booth after standardized instruction in a single session as part of a larger test battery study. Written informed consent was obtained from all participants. The study was part of the project "Automatic hearing diagnostics and non-cooperative hearing aid adaption," which was approved by the local ethics committee of the University hospital rechts der Isar of the Technical University of Munich, Germany, and is in accordance with the Declaration of Helsinki.

## 2.2 | Questionnaires

### 2.2.1 | Questionnaire for auditory tests according to DIN EN ISO 389-9:2009–12

This questionnaire is part of the audiometric standard DIN EN ISO 389-9:2009–12 (DIN Deutsches Institut & für Normung e.V., 2009).

It is usually used to exclude potentially hearing-impaired participants in the calibration process of auditory devices. Twelve questions cover ENT history (otologic diseases, ear operations), risk factors for hearing impairment (ototoxic drugs, noise exposition), and family history (relatives with hearing impairment). We included this questionnaire in our study in order to assess a basic standardized ENT history and potential exclusion criteria (see Table 1). The results of this questionnaire will not be discussed in detail.

#### 2.2.2 | Hearing handicap inventory for the elderly-Screening version

The Hearing Handicap Inventory for the Elderly (HHIE; Ventry and Weinstein (1982); Weinstein and Ventry (1983)) in its self-assessed screening version with 10 questions (HHIE-S; Ventry and Weinstein (1983); Weinstein (1986)) evaluates subjective hearing impairment, which can significantly differ from audiologic hearing impairment. Depending on the answers, a score is calculated and assigns individuals to different subjective handicap categories: no (score 0–8), mild-to-moderate (score 10–24), and severe (score 26–40) hearing handicap (American Speech-Language-Hearing-Association, 1997, 2016). We used the HHIE-S in its German version (Bertoli et al., 1996) on a handheld touch screen device (Sentiero Advanced, PATH MEDICAL GmbH, Germering, Germany).

### 2.3 | Otoscopy and tympanometry

Each participant was screened otoscopically to rule out relevant pathologies of the outer ear canal and the tympanic membrane. Conventional 226 Hz-tympanometry was then performed before all other measurements to assess middle ear function. Significant alterations led to exclusion of the participant (see Table 1).

### 2.4 | Pure-tone audiometry

Pure-tone audiometric air conduction thresholds for both ears were obtained at 250, 500, 1,000, 2,000, 4,000, 6,000, and 8,000 Hz. Two calibrated devices were used dependent on availability: The Otobox, an audiometric platform developed by the Experimental Audiology of the ENT Department of the University hospital rechts der Isar, in combination with Beyerdynamic DT 48 headphones, or the Sentiero Advanced (PATH MEDICAL GmbH, Germering, Germany) with Sennheiser HDA 280 headphones. Both devices comply to the normative criteria for diagnostic audiometers according to DIN EN 60645–1:2002–09 and apply an automatic threshold determination according to the standard DIN EN ISO 8253-1:2011–04 (DIN Deutsches Institut & für Normung e.V., 2002, 2011). Hearing thresholds determined group assignment to HC, NHE, or HIE and had to be in accordance with certain inclusion criteria (see Table 1).

### 2.5 | Distortion product otoacoustic emission thresholds

Distortion product otoacoustic emissions (DPOAEs) arise from the active, nonlinear cochlear amplifying process of the outer hair cells (OHCs), when the ear is stimulated simultaneously by two tones with neighboring frequencies ($f_1$ and $f_2$). The cubic distortion product ($2f_1$-$f_2$; $f_2$:$f_1$ = 1.2) represents OHC integrity in the area of the characteristic place of $f_2$ (Janssen & Müller, 2008, pp. 412–422). Stimulation was steered via the Otobox and applied via an Etymotic Research ER-10C ear probe consecutively in both ears. Level ratio of the primary tones $L_1$ = .4 $L_2$ + 39 dB was set in accordance with the "scissor" paradigm by Kummer et al., which yields highest cubic DPOAE levels (Janssen, 2009; Kummer et al., 2000). The DPOAE-level ($L_{dp}$) was measured after an in-the-ear calibration of the ear probe for systematically varied $L_2$ levels, starting with $L_2$ = 60 dB SPL and decreasing $L_2$ by 10 dB SPL after measurement of a valid DPOAE or increasing $L_2$ by 5 dB SPL after failure of a valid DPOAE measurement. Maximum $L_2$ level was set to 70 dB SPL to avoid technical distortion of the ear probe. Like this a series of $L_2$-$L_{dp}$ pairs was generated for a fixed $f_2$-frequency, which was plotted in a semilogarithmic diagram (*x*-axis: $L_2$, *y*-axis: sound pressure level $L_{dp}$). The DPOAE threshold was defined as the $L_2$ of the intersection point of the linear regression line of the above mentioned measuring points with the x-axis, where $L_{dp}$ is zero. When less than three valid $L_2$-$L_{dp}$ pairs were measurable, the DPOAE threshold was defined as the lowest $L_2$ with a valid DPOAE (for more details of this extrapolation method, see Boege and Janssen (2002); Rosner (2011, p. 124)). DPOAE thresholds were assessed successively for $f_2$ = 1.5, 2, 3, 4, 6, and 8 kHz. The 6 and 8 kHz results, however, have to be interpreted with special caution as standing waves in the ear canal may affect their accuracy (Janssen, 2009; Mrowinski & Scholz, 2011).

### 2.6 | Auditory brainstem response

Auditory brainstem response (ABR) measurements were integrated in our study to evaluate integrity of the auditory nerve and the auditory brainstem. The ABR module of the portable Sentiero Advanced device (PATH MEDICAL GmbH, Germering, Germany) was used with a 100 µs rectangular click (.7–6 kHz) stimulus. Electrodes were placed on vertex (+) and ipsilateral mastoid (−), the mass electrode on the forehead. Stimulus rate was set to 20 Hz; a jitter function slightly varied the stimulus rate in order to minimize electric interference and adaption of the auditory system. One click series of 70 dB click level and two series of 80 dB click level were applied to each ear via insert earphones (otoInsert, GN Otometrics, Taastrup, Denmark) with 4,000 repetitive stimuli, respectively. Participants completed ABR measurements in a soundproof and electromagnetically shielded booth in a relaxed lying position and were advised to snooze. For the final evaluation, waves I to V for each click series were marked in the ABR software module of the Sentiero Advanced device. Peak-to-peak-amplitudes of wave I were calculated as a surrogate

of the integrity of cochlear synapses with the auditory nerve fibers (Mrowinski, 2009). As absolute latencies and amplitudes of ABR measurements strongly depend on the individual's sensation level (Lehnhardt & Laszig, 2009) and as a physical or statistical compensation for hearing loss was difficult due to the broadband spectrum of the stimulus, we calculated interpeak latencies of waves I–V (IPL I–V), I–III (IPL I–III), and III–V (IPL III–V) for the main ARHL analyses (wave delay due to hearing loss will affect all waves equally which should result in essentially constant interpeak latencies). The average of both 80 dB series was defined as the participant's final result. The 70 dB series was only used to ease wave identification in the 80 dB series by comparing latencies and waveforms.

## 2.7 | Central auditory discrimination performance tests

The fundamental features frequency, intensity, and duration of a sound are basically encoded by activity and location of the cochlear hair cells and the firing rates of auditory nerve fibers (Neumann & Rübsamen, 2005; Pickles, 2015). They are finally processed, discriminated, and set to consciousness in the central auditory nervous system (Trepel, 2008). Therefore, procedures aiming at just noticeable stimulus differences (JNDs) can test certain aspects of central auditory processing. In 2004, Bungert-Kahl et al. presented a straightforward three-alternative forced-choice paradigm for the assessment of central JNDs, in which one test signal differs from two reference signals in a signal triplet with respect to the features mentioned above. By varying the magnitude of the signal difference in accordance with a certain algorithm in successive trials, the individual's JND can be obtained. Different test modes (see below) can be used to provide topodiagnostic specificity (Bungert-Kahl et al., 2004; Freigang et al., 2011; Ludwig, 2009).

We adapted this test to the needs of our study and developed a special operational interface for the Sentiero Advanced device. In each trial, participants listened to a signal triplet consisting of one deviant test signal and two reference signals via Sennheiser HDA 280 headphones. The position of the deviant test signal within the signal triplet was randomized. The signal triplet was represented by a row of three playing cards on the touch screen of the Sentiero Advanced device. The participant had to identify the two identical reference signals, which were then chosen on the touch screen by turning the respective playing cards (just as if playing a memory game). In each trial participants could play back the signal triplet as often as needed; if they could not identify the identical signals, they were encouraged to guess. JNDs were obtained for the stimulus parameters frequency, level, and duration in different test modes (see below). The JND for each parameter and test mode was assessed separately in a series of trials. The main idea of this test paradigm was to provide an identical operational concept independent of stimulus parameter and test mode.

The magnitude of the stimulus difference (frequency: $\Delta f$, level: $\Delta L$, and duration: $\Delta t$) between test and reference signal was varied between the consecutive trials according to a specially designed adaptive algorithm: Starting at a clearly audible difference, the stimulus difference was reduced in the first three trials after each correct choice (*One-down-principle*). Like this the participant's JND was approached more quickly. After the third trial, the stimulus difference $\Delta f/\Delta L/\Delta t$ was only reduced after two correct answers in two successive trials with identical stimulus differences (*Two-down-principle*), whereby the probability to attain low JNDs just by guessing (33% in each trial) was significantly decreased to $(33\%)^2 = 11\%$. One incorrect answer resulted in an increase of the stimulus difference during the whole test procedure (*One-up-principle*). Altogether, in this algorithm the stimulus difference oscillated around the participant's actual difference limen, as trials with stimulus differences below the participant's JND will usually result in an incorrect answer (and, like this, create a preliminary minimum of the stimulus difference) and trials with stimulus differences above the participant's JND will usually lead up to two correct answers (and, like this, create a preliminary maximum of the stimulus difference). Having reached three minima and three maxima or 42 trials, the procedure stopped. In order to obtain the participant's JND, medians of the minima and of the last two maxima were calculated, respectively. The JND was defined as the mean of the two medians.

In a series of correctly answered trials, the magnitude of the stimulus difference was successively decreased according to a randomized algorithm, whereas in a series of incorrectly answered trials, it was successively increased in randomized steps. Like this theoretically every JND could be attained.

The different test modes were used to achieve topodiagnostic specificity (Biedermann et al., 2008; Bungert-Kahl et al., 2004; Freigang et al., 2011; Ludwig, 2009):

In the *dichotic* test mode, both ears received different stimuli. Only one ear was stimulated by the signal triplet consisting of one test and two reference signals. Simultaneous to those three tonal signals, three broadband noise signals were presented to the other ear. The noise signals mask central auditory processing of the tonal signals in the hemisphere contralateral to the noise (and ipsilateral to the tonal signals) and, in this way, lead up to a kind of unilateral representation of the tonal signals in the hemisphere contralateral to the tonal signals (and ipsilateral to the noise signals). Furthermore, experiments showed that dichotic test results are not influenced by brainstem lesions. Dichotic tests therefore enable separate and selective testing of auditory discrimination performance of both hemispheres, which, under physiologic conditions, is not possible due to the bilateral input of both hemispheres (Biedermann et al., 2008; Bungert-Kahl et al., 2004). Dichotic frequency discrimination tasks assess the integrity of the tonotopic organization of the tested hemisphere, dichotic level, and duration discrimination tasks unilateral hemispherical intensity and temporal processing (Freigang et al., 2011; Hackett, 2015; Neumann & Rübsamen, 2005).

In contrast, in the *interaural* test mode, tonal signals are presented to both ears. The noise triplet of the dichotic procedures is replaced by a triplet of reference signals. Input of both ears is always identical with the exception of the test signal, which is only presented to the

test ear. Due to the central fusion of the bilateral tonal signals (and stimulation of central sound localization mechanisms, which also rely on frequency/phase, level and duration differences), interaural tests create a special spatial effect: that is, the reference signal pairs are centered in the head, whereas the test-and-reference-signal pair results in a lateralization effect (to the shorter signal in case of the duration tests, to the louder signal in case of the level tests) or an impression of sound spreading (in case of the frequency tests). A specificity of interaural tests for brainstem auditory performance was shown in prior studies that refute an influence of di- and telencephalic lesions on test results (Biedermann et al., 2008; Bungert-Kahl et al., 2004; Freigang et al., 2011; Ludwig, 2009). Interaural frequency discrimination tasks assess motion detection, interaural level, and duration discrimination tasks sound localization in the horizontal plane in the brainstem (Middlebrooks, 2015).

In addition to the original test protocol by Bungert-Kahl et al. (2004), a *binaural* test mode was launched, in which both ears simultaneously receive the same signal triplet consisting of one test and two reference signals. As no topodiagnostic specificity is known, this test mode was only used as training for the dichotic and interaural tests. Results will not be discussed.

The JNDs were assessed for each stimulus parameter (frequency, level, and duration) for binaural, interaural, and dichotic test mode, respectively. For the interaural and dichotic test mode, a separate JND was obtained for right and left ears, whereby the side relates to the ear where the test signal is presented. A randomized order was utilized for the whole study collective for the interaural and the dichotic test mode and the individual stimulus parameters to avoid systematic learning or tiring effects. Binaural procedures were constantly used first as a kind of training. Stimulus frequency of the reference signals was always 1 kHz at 40 dB SL (reference was the 1 kHz-PTA-threshold), like this accounting for differences in audibility between participants with normal and impaired hearing. The deviant test signal differed from the reference signals by $\Delta f$ (higher), $\Delta L$ (louder), or $\Delta t$ (shorter). The noise signal consisted of broadband noise (up to 8 kHz) at 40 dB SL. Except from the deviant signal in the duration discrimination tasks, all signals lasted for 400 ms and the inter-signal-interval was 600 ms (for further details on the algorithm and the signals, see also Pürner, 2019).

## 2.8 | Speech in noise—Oldenburger Satztest

The Oldenburger Satztest/Oldenburg Sentence Test (OLSA), a German speech-in-noise test developed 1999 by Wagener et al. (1999a, 1999b, 1999), assesses speech understanding in standardized noise by presenting randomized German five-word-sentences consisting of name, verb, numeral, adjective, and object (e.g., Thomas kauft 7 rote Schuhe = Thomas buys seven red shoes) out of a thesaurus of 10 words per part of speech, respectively. Each test list consists of 30 sentences. The signal-to-noise ratio (SNR), the difference between speech and noise level, varies between the consecutive sentences dependent on the proportion of words correctly identified in the sentence before. Finally, a theoretical speech reception threshold $L_{50}$ (SRT $L_{50}$), the SNR corresponding to 50% intelligibility, is calculated by averaging the SNRs of the last 20 sentences. Healthy individuals on average achieve a speech reception threshold $L_{50}$ of −7.1 dB SNR, that is they achieve 50% intelligibility when the noise is presented 7.1 dB louder than speech level.

The OLSA module was implemented on a Siemens Unity 2-Audiometer in combination with Canton CD 310 free field loudspeakers. The participant's head was centered between the loudspeakers. Noise level was fixed to 65 dB SPL as in the original version of Wagener et al. (1999b), speech level was automatically adapted. One training list was provided before the final measurement.

## 2.9 | Statistical analysis

All statistical analyses were performed with MATLAB (Version 2015b, MathWorks, USA) and in accordance with recommendations of the Institute for Medical Informatics, Statistics and Epidemiology (IMedIS) of the Technical University of Munich. (1) In a first step, all test results gathered separately for right and left ear (PTA, dichotic and interaural CADP tests, DPOAE threshold, ABR) were reduced to one final result by forming means. This is necessary, as test data of the right and the left ear are not independent and could elicit false significance in statistical analyses requiring independent data, if right and left ear results were used separately (Weiß, 2013). When valid test results were available only for one ear or when methods obtained only one result per participant (OLSA), this result was taken as final. (2) Statistics were evaluated on a significance level $p$ of 5%. (2a) Means and standard deviations for the three groups (HC, NHE, and HIE) were calculated from the final results for metric tests (PTA, CADP tests, OLSA, DPOAE thresholds, and ABR) and analyzed with respect to significant differences by ANOVA and Tukey HSD as post hoc test with inherent correction for multiple testing (*multcompare*-tool of MATLAB). When comparing NHE and HIE, an additional ANOCOVA (covariable: age) was performed to take into consideration a slight age difference between both groups. In special cases (explained in the Results), we additionally performed an ANOCOVA controlling for high-frequency hearing loss between the HC and the NHE group (covariable: average hearing loss at 6 an 8 kHz of both ears). For the ordinally scaled HHIE-S, the Kruskal–Wallis test was used. (2b) If clinically or statistically relevant, results were correlated by Spearman's Rho.

As no data for the CADP test were available for comparable study cohorts and procedures, an exact power analysis could not be done prior to the study. Instead, we defined the final group size $n = 30$ by trying to estimate the maximally recruitable NHE group size at our center by analyzing our ENT database. The rationale for this procedure was that it is most challenging to find normally hearing elderly in accordance with our strict definition in a general population. All data, including outliers in the graphs, were considered in the statistical analyses.

## 3 | RESULTS

### 3.1 | Participants' characteristics

Overall, 90 out of 97 participants could be included in the final analyses. Each group (HC, NHE, and HIE) consisted of 30 participants—15 male and 15 female subjects.

Mean age ± *SD* of the HC group was 24.2 ± 1.7 years, mean ages of the NHE and the HIE group were 66.7 ± 4.2 and 73.2 ± 4.2 years, respectively. Due to this slight but significant (ANOVA, $F_{2, 87} = 1666.9$, $p < .001$; post hoc test Tukey HSD, $p < .001$) unintended age difference between the NHE and the HIE group, we additionally performed an ANOCOVA (see Section 2.9) for comparisons between NHE and HIE results to rule out interfering age effects. Male and female subjects had very similar age distributions in each group (HC: 24.6 ± 1.8 vs. 23.8 ± 1.6 years; NHE: 66.5 ± 4.6 vs. 66.9 ± 3.9 years; and HIE: 72.9 ± 4.6 vs. 73.6 ± 3.9 years; male results are listed first).

The average hearing loss ± *SD* at the PTA-frequencies 500, 1,000, 2,000, and 4,000 Hz on both ears (PTA500-4000 Hz), which was, in addition to age, used for group assignment, was 2.9 ± 3.1 dB HL in the HC , 9.1 ± 5.2 dB HL in the NHE, and 33.4 ± 5.9 dB HL in the HIE group. Again, men and women had very similar results in each group (HC: 3.1 ± 3.0 vs. 2.6 ± 3.3 dB HL; NHE: 9.6 ± 4.3 vs. 8.7 ± 6.1 dB HL; and HIE: 33.2 ± 6.3 vs. 33.7 ± 5.7 dB HL; male results listed first). Due to this similarity and the equivalent age distributions, we did not differentiate between male and female results in all further group analyses. All three groups (including HC and NHE) had a significantly different average PTA500-4000 Hz (ANOVA, $F_{2, 87} = 328,7$, $p < .001$; post hoc test Tukey HSD, $p < .001$), which is a quite common problem in studies comprising "normally hearing" elderly (due to WHO-definition), as it is nearly impossible to recruit elderly without any high-frequency hearing loss. As both HC and NHE nevertheless fulfilled the slightly modified WHO criteria for normal hearing performance, we did not statistically consider this PTA-difference in our primary analyses. Only in special cases (described in the following parts of the Results section), an additional ANOCOVA was used to assess the effects of this PTA differences. Pure-tone audiometric air conduction thresholds over the whole frequency range and significant differences between the groups are shown in Figure 1. The NHE group was characterized by a slight high-frequency hearing loss, which was much more expressed in the HIE group.

The average HHIE-S-score increased significantly from the HC group to the NHE group (Kruskal–Wallis test, $\chi^2 = 38.2$, $p < .001$; post hoc test Tukey HSD, $p < .001$) and from the NHE group to the HIE group ($p = .014$). The mean HHIE-S-score ± SD was 2.7 ± 2.7 in the HC, 9.1 ± 6.9 in the NHE, and 17.1 ± 10.1 in the HIE group. In the HHIE-S-categorization, an average participant of the HC group therefore negated any subjective hearing impairment. The NHE subjects on average perceived no or only a mild hearing impairment, whereas the HIE subjects on average reported a mild-to-moderate hearing handicap. Variability of the answers increased between the three groups, as shown by the standard deviation of the score.

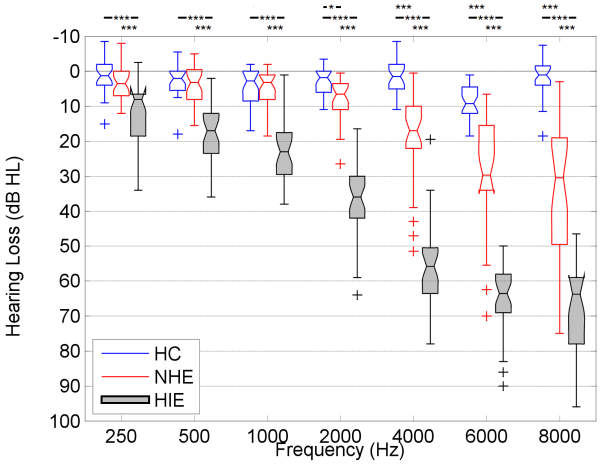


**FIGURE 1** Pure-tone audiometric thresholds. The healthy controls (HC) group was characterized by a flat and unimpaired audiometric threshold over the whole frequency range. The normally hearing elderly (NHE) group had a slight high-frequency hearing loss which was much more expressed in the hearing-impaired elderly (HIE) group. The HC and NHE groups differed significantly from the HIE group at all frequencies, whereas significant differences between the HC and NHE group were observable only in higher frequencies above 2000 Hz (ANOVA, $F_{2, 87} = 19.6$ (250 Hz)/53.1 (500 Hz)/79.0 (1000 Hz)/174.3 (2000 Hz)/201.5 (4000 Hz)/188.2 (6000 Hz)/171.8 (8000 Hz), $p < .001$ in all cases; post hoc test Tukey HSD). *$p < .05$; **$p < .01$; ***$p < .001$. Notches in the boxes show the 95% confidence interval

### 3.2 | DPOAEthresholds

As DPOAEs are only measurable up to about 50 dB hearing loss in PTA (Thomas Janssen & Müller, 2008; Mrowinski & Scholz, 2011) and many participants of the HIE group exceeded this limit mainly at higher frequencies, calculating average DPOAE thresholds in this group will underestimate the real OHC dysfunction by not considering hearing impaired participants without measurable DPOAE thresholds. Even so a significant increase of the average DPOAE threshold at all frequencies from 1.5 to 4 kHz could be observed when comparing the results of the HC, NHE, and HIE group, ranging from about 12–15 dB SPL in the HC group to up to 56 dB SPL at 4 kHz of the HIE group (see Figure 2 and Table 2). For 6 and 8 kHz, a significant increase was existent only between the HC and the NHE group, but not between both elderly groups. Abovementioned physiological limitations of the method were reflected in a decreasing rate of valid DPOAE thresholds from the HC and NHE group to the HIE group, especially at higher frequencies. Besides potential problems with standing waves in the ear canal at 6 and 8 kHz (Janssen, 2009; Mrowinski & Scholz, 2011), the resulting small sample size can affect the results and the comparison between the NHE and HIE group at 6 and 8 kHz.

Due to the slight but partly significant (ANOVA, $p < .001$ for 4, 6 and 8 kHz, see Figure 1) difference in PTA-thresholds between the HC and NHE group, a strict separation between age and auditory status effects on DPOAE thresholds was not possible at first view. A subgroup of the NHE group with PTA-thresholds

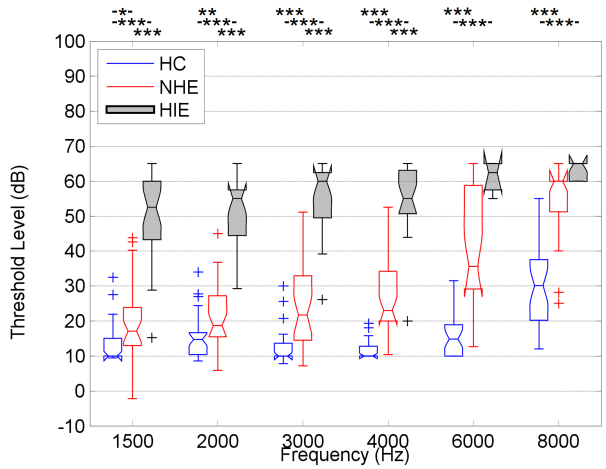


**FIGURE 2** DPOAE thresholds. A significant deterioration of DPOAE thresholds between the healthy controls (HC), the normally hearing elderly (NHE), and the hearing-impaired elderly (HIE) group was seen at 1.5, 2, 3, and 4 kHz and between the HC and the NHE group at 6 and 8 kHz. Separating aging- and hearing loss-associated effects, however, is difficult due to high-frequency hearing loss of the NHE group and small sample sizes for some of the HIE results. For statistical methods, please refer to Table 2. $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$. Notches in the boxes show the 95% confidence interval

below 15 dB HL at frequencies relevant for the DPOAE thresholds was therefore selected, consisting of the eight best-hearing NHE participants (NHE15dB; considered frequencies: 1 to 4 kHz). In doing this, the DPOAE thresholds of this subgroup (and also PTA-thresholds from 250 Hz to 4000 Hz) no longer differed significantly from the HC group but were still significantly different from those of the HIE group (ANOVA, $p < .001$, respectively, see Table 2). For 6 and 8 kHz, an analogous procedure was impossible, as only one individual of the NHE group was characterized by PTA-thresholds below 15 dB HL at 6 and 8 kHz, precluding meaningful statistics. Instead, we statistically eliminated the difference in audibility at 6 and 8 kHz by means of an ANOCOVA (covariable: average hearing loss at 6 and 8 kHz of both ears) still showing significant differences in DPOAE thresholds at these frequencies between the HC and the NHE group.

## 3.3 | Auditory brainstem response

The interpeak latency I–V, which represents retrocochlear sound conduction up to midbrain structures, was significantly higher in both elderly groups (NHE and HIE) in comparison to the HC group, but did not significantly differ between both elderly groups. A more detailed analysis could not detect any significant differences between the interpeak latency I–III of all three groups, which physiologically reflects sound processing in the auditory nerve and cochlear nucleus. In contrast, the interpeak latency III–V, which is determined by brainstem sound processing, increased significantly from the HC group to both elderly groups, but not between both elderly groups (analogous to IPL I–V, see Figure 3 and Table 3).

In order to evaluate the integrity of the cochlear synapses, an analysis of the ABR amplitude for wave I was performed. A significant decrease between all three groups could be demonstrated after controlling for the age difference between both elderly groups by an ANOCOVA (covariable: age, see Figure 4). Controlling for the audibility differences between the HC and the NHE group was neither methodically nor statistically (by an ANOCOVA) feasible in a reliable manner due to the broadband nature of the stimulus.

## 3.4 | Central auditory discrimination performance

### 3.4.1 | Level discrimination and duration discrimination

In all dichotic and interaural level and duration discrimination tasks, a significant increase of the average JNDs could only be observed between the healthy controls (HC) and both elderly groups (NHE and HIE), but not between both elderly groups. Interestingly the HIE group could achieve slightly better average JNDs in all trials compared to the NHE group, possibly due to recruitment phenomena. Figure 5 and Table 4 provide a detailed survey of all results. Average JNDs for duration discrimination ranged from 35.1 to 86.7 ms, that means from 8.8% to 21.7% of the basic stimulus length. For level discrimination, average results were 2.7 to 5.1 dB; analogous percentages cannot be provided due to the individually set stimulus level (40 dB SL).

### 3.4.2 | Frequency discrimination

In contrast, the results of the frequency discrimination tasks showed different behavior (see Figure 5c and Table 4). The average dichotic and interaural JNDs for frequency discrimination were lowest for the HC group, higher for the NHE group and highest for the HIE group. A statistically significant JND-increase could be observed between the HIE group and both normally hearing groups (HC and NHE), whereas the NHE group was characterized by a non-significant but strong tendency to higher JNDs in comparison to the HC group in the ANOVA. With the exception of the HC group, *dichotic* and *interaural* tasks provided quite similar average JNDs, ranging from 2.3 to 21.8 Hz, that means .23% to 2.18% of the stimulation frequency.

Results of the binaural test mode for level, duration, and frequency discrimination are not mentioned, as this test mode was only used for training purposes.

In order to rule out that CADP test results were just determined by pure-tone audiometric thresholds, Spearman's Rho between all test modes/stimulus parameters and the PTA-threshold

**TABLE 2** DPOAE thresholds

| Group | 1.5 kHz | 2 kHz | 3 kHz | 4 kHz | 6 kHz | 8 kHz |
|---|---|---|---|---|---|---|
| HC | 13.6 ± 6.0 ($n$ = 30) | 15.4 ± 6.3 ($n$ = 30) | 13.0 ± 5.2 ($n$ = 30) | 11.9 ± 3.0 ($n$ = 30) | 16.4 ± 6.7 ($n$ = 30) | 30.8 ± 12.4 ($n$ = 30) |
| NHE | 20.8 ± 11.2 ($n$ = 29) | 23.4 ± 12.1 ($n$ = 29) | 24.7 ± 12.8 ($n$ = 29) | 27.0 ± 11.1 ($n$ = 29) | 41.2 ± 17.2 ($n$ = 27) | 53.9 ± 12.4 ($n$ = 17) |
| HIE | 50.6 ± 12.1 ($n$ = 27) | 51.9 ± 10.9 ($n$ = 23) | 55.3 ± 10.1 ($n$ = 20) | 56.1 ± 10.2 ($n$ = 21) | 63.3 ± 2.9 ($n$ = 3) | 62.2 ± 2.6 ($n$ = 9) |
| $p$-values (Comparison HC NHE HIE) | ANOVA: HC NHE: .021* HC HIE: <.001*** NHE HIE: <.001*** ANOCOVA: NHE HIE: <.001*** | ANOVA: HC NHE: .0085* HC HIE: <.001*** NHE HIE: <.001*** ANOCOVA: NHE HIE: <.001*** | ANOVA: HC NHE: <.001*** HC HIE: <.001*** NHE HIE: <.001*** ANOCOVA: NHE HIE: <.001*** | ANOVA: HC NHE: <.001*** HC HIE: <.001*** NHE HIE: <.001*** ANOCOVA: NHE HIE: <.001*** | ANOVA: HC NHE: <.001*** HC HIE: <.001*** NHE HIE: .014* ANOCOVA: HC NHE: <.001*** NHE HIE: .63 | ANOVA: HC NHE: <.001*** HC HIE: <.001*** NHE HIE: .019 ANOCOVA: HC NHE: <.01** NHE HIE: .52 |
| NHE15dB | 16.5 ± 7.4 ($n$ = 8) | 17.4 ± 6.0 ($n$ = 8) | 17.2 ± 5.5 ($n$ = 8) | 17.8 ± 5.8 ($n$ = 8) | 35.7 ± 18.3 ($n$ = 8) | 44.6 ± 17.0 ($n$ = 5) |
| $p$-values (Comparison HC NHE15dB-HIE) | ANOVA: HC NHE15dB: .71 HC HIE: <.001* NHE15dB HIE: <.001* | ANOVA: HC NHE15dB: .82 HC HIE: <.001* NHE15dB HIE: <.001* | ANOVA: HC NHE15dB: .31 HC HIE: <.001* NHE15dB HIE: <.001* | ANOVA: HC NHE15dB: .086 HC HIE: <.001* NHE15dB-HIE: <.001* | Not calculated | Not calculated |

*Note*: Mean ± *SD* (dB SPL) and $p$-values for each group-wise comparison between the healthy controls (HC), the normally hearing elderly (NHE), and the hearing-impaired elderly (HIE) group. At first view, a significant deterioration of DPOAE thresholds at all frequencies is visible between the HC, NHE, and HIE group (ANOVA, $F_{2, 83} = 105.8$ (1.5 kHz)/$F_{2, 79} = 93.0$ (2 kHz)/$F_{2, 76} = 114.0$ (3 kHz)/$F_{2, 77} = 162.4$ (4 kHz)/$F_{2, 57} = 38.8$ (6 kHz)/$F_{2, 53} = 37.1$ (8 kHz), $p < .001$ in all cases; post hoc test Tukey HSD), the only exception being 6 and 8 kHz, where the ANOCOVA considering age differences did not show significant differences between NHE and HIE (ANOCOVA, $F_{1, 53} = 46.7$ (1.5 kHz)/$F_{1, 49} = 42.9$ (2 kHz)/$F_{1, 46} = 38.7$ (3 kHz)/$F_{1, 47} = 37.8$ (4 kHz)/$F_{1, 27} = .23$ (6 kHz)/$F_{1, 23} = .43$ (8 kHz), $p = .63$ (6 kHz)/.52 (8 kHz)). In order to eliminate audibility effects between the HC and the NHE group, a special NHE15dB subgroup was introduced, characterized by PTA-thresholds below 15 dB HL at 1 to 4 kHz. DPOAE thresholds of this subgroup (and also PTA-thresholds from 250 Hz to 4000 Hz) no longer differed significantly from the HC group but were still significantly different from those of the HIE group (ANOVA, $F_{2, 62} = 123.0$ (1.5 kHz)/$F_{2, 58} = 134.2$ (2 kHz)/$F_{2, 55} = 212.3$ (3 kHz)/$F_{2, 56} = 274.1$ (4 kHz), $p < .001$ in all cases; post hoc test Tukey HSD). It remains unclear whether this is a physiological or statistical effect due to small sample size. For 6 and 8 kHz (as only one NHE-individual had PTA-thresholds below 15 dB), we statistically eliminated audibility differences between HC and NHE by means of an ANOCOVA (covariable: average hearing loss at 6 an 8 kHz of both ears, $F_{1, 54} = 25.9$ (6 kHz)/$F_{1, 44} = 9.0$ (8 kHz), $p < .001$ (6 kHz)/$p = .0043$ (8 kHz)) still showing significant differences between these groups. Be aware of the decreasing sample sizes in higher frequencies and hearing impaired subjects due to physiological limitations of the DPOAE measurements. *$p < .05$; **$p < .01$; ***$p < .001$. $n$: number of valid measurements.

at 1 kHz (the stimulation frequency of the test) was calculated. All calculations revealed low correlation coefficients (.11 to .42; not significant for level discrimination, all other results significant at least at $p < .05$). As it is known that high-frequency hearing loss above 4 kHz can affect sound localization (Hornsby et al., 2011; Middlebrooks, 2015) and as the CADP tests partly stimulate sound localization mechanisms, an additional ANOCOVA was performed taking into account differences in high-frequency hearing loss between the HC and the NHE group (covariable: average hearing loss at 6 an 8 kHz of both ears). For level and duration discrimination tests, the former results for the HC and the NHE group were confirmed—the only exception being interaural duration discrimination ($p = .07$, scarcely not significant anymore). For frequency discrimination, upper mentioned strong tendency toward increasing JNDs between the HC and the NHE group could be confirmed in a statistically significant manner.

### 3.5 | Oldenburger Satztest/Oldenburg sentence test

As expected, the HC group obtained the best OLSA results (see Figure 6). The average SRT $L_{50}$ (±*SD*) was −8.5 ± .5 dB SNR and even better than the reference value at −7.1 dB SNR. Practically, this means that the average participant of the HC group could achieve 50% intelligibility when the background noise was 8.5 dB louder than the sentence being presented. The NHE group lay slightly worse and slightly below the reference value, with an average SRT $L_{50}$ of −6.9 ± .8 dB SNR. The average SRT $L_{50}$ of the HIE group was −4.8 ± 1.5 dB SNR. The average results of all three groups differed significantly in the statistical analyses (ANOVA, additional ANOCOVA for NHE and HIE (covariable: age), $p < .001$, respectively; see Figure 6). As speech understanding in noise is affected by high-frequency hearing loss (Hornsby et al., 2011) and as the "normally

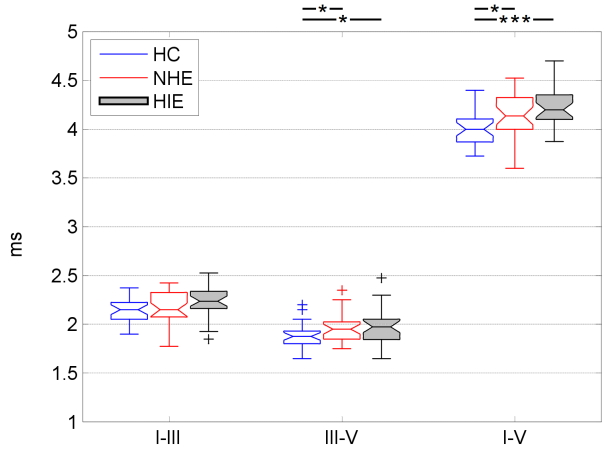


FIGURE 3 ABR interpeak latencies. Interpeak latencies I–III, III–V, and I–V for the healthy controls (HC), the normally hearing elderly (NHE), and the hearing-impaired elderly (HIE) group. Only the central transmission time (III–V) showed a significant deterioration in both elderly groups (compared to the young and healthy control group), leading up to an analogous increase in the interpeak latency I–V. For statistical details, please refer to Table 3. *$p < .05$; **$p < .01$; ***$p < .001$. Notches in the boxes show the 95% confidence interval

hearing" HC and NHE groups were characterized by different grades of high-frequency hearing impairment, an additional ANOCOVA was performed (covariable: average hearing loss at 6 an 8 kHz of both ears), confirming the results of the ANOVA.

## 4 | DISCUSSION

The present cross-sectional study provides evidence for alterations in peripheral and central sound processing of the auditory system in ARHL. By means of a three-group-sample and a topodiagnostic test battery, we aimed at separating age- and hearing loss-related changes in performance of all sections of the auditory system. A multimodal concept was used to draw representative samples of normally hearing young controls (HC), normally hearing elderly (NHE), and hearing-impaired elderly (HIE). For defining auditory status, we applied slightly adapted WHO grades of hearing impairment (Mathers et al., 2000; Olusanya et al., 2019; World Health Organization, 1991).

Even though the whole ENT database of the University hospital rechts der Isar in a large city like Munich was scanned automatically, it was a main challenge of this study (as in many other similar studies) to gain a sufficient number of normally hearing elderly. Indeed, a comparison with international normative data of hearing threshold distributions according to DIN EN ISO 7029:2017–06 could prove that our NHE group mainly represented the best-hearing quartile of an average elderly population; the HIE group, in contrast, the worst quartile (DIN Deutsches Institut & für Normung e.V., 2017). Nevertheless, a significant difference in the average PTA500-4000 Hz between the young HC and the elderly NHE group had to be taken into account due to a high-frequency hearing loss of the NHE group, although both groups met the adapted (and in this way stricter) WHO criteria for "no hearing impairment."

### 4.1 | OHC activity—DPOAEthresholds

Numerous trials have already aimed at separating age- and hearing loss-related alterations of OHC function in ARHL by means of DPOAEs. The majority of recent studies agrees that age-related hearing loss is associated with a decrease in *DPOAE levels* (Abdala & Dhar, 2012; Cilento et al., 2003; Hoth et al., 2010; Keppler et al., 2010; Oeken et al., 2000; Profant et al., 2019; Uchida et al., 2008). Independent age effects on DPOAEs, however, remain controversial. Some authors assume those effects (Uchida et al., 2008), some attribute observed decreases in DPOAE levels to both age and hearing loss (Keppler et al., 2010; Oeken et al., 2000),

TABLE 3 ABR interpeak latencies

| Group | IPL I–III | IPL III–V | IPL I–V |
|---|---|---|---|
| HC | 2.14 ± 0.12 ($n = 29$) | 1.87 ± 0.14 ($n = 29$) | 4.01 ± 0.17 ($n = 29$) |
| NHE | 2.18 ± 0.16 ($n = 30$) | 1.97 ± 0.14 ($n = 30$) | 4.14 ± 0.22 ($n = 30$) |
| HIE | 2.23 ± 0.16 ($n = 28$) | 1.97 ± 0.18 ($n = 29$) | 4.22 ± 0.21 ($n = 28$) |
| *p*-values | *ANOVA*: .079<br>(HC NHE: .70; HC HIE: .068; NHE HIE: .31)<br>*ANOCOVA*:<br>NHE HIE: .41 | *ANOVA*:<br>HC NHE: .0498*<br>HC HIE: .032*<br>NHE HIE: .98<br>*ANOCOVA*:<br>NHE HIE: .93 | *ANOVA*:<br>HC NHE: .043*<br>HC HIE: <.001***<br>NHE HIE: .34<br>*ANOCOVA*:<br>NHE HIE: .81 |

*Note*: Mean ± *SD* (ms) and *p*-values for each group-wise comparison between the healthy controls (HC), the normally hearing elderly (NHE), and the hearing-impaired elderly (HIE) group. A significant prolongation of ABR interpeak latencies I–V and I–III could be observed between the HC and both elderly groups (NHE and HIE) but not between the two elderly groups, suggesting that aging (and not hearing loss) affects signal transduction in the brainstem (ANOVA, $F_{2, 84} = 2.6$ (IPL I–III)/$F_{2, 85} = 4.1$ (IPL III–V)/$F_{2, 84} = 7.4$ (IPL I–V), $p = .079$ (IPL I–III)/$p = .019$ (IPL III–V)/$p = .0011$ (IPL I–V); post hoc test Tukey HSD). Also, after controlling for a slight age difference between the NHE and the HIE group, no significant differences in IPLs could be demonstrated (ANOCOVA, $F_{1, 55} = .69$ (IPL I–III)/$F_{1, 56} = .007$ (IPL III–V)/$F_{1, 56} = .057$ (IPL I–V), $p = .41$ (IPL I–III)/$p = .93$ (IPL III–V)/$p = .81$ (IPL I–V)). *$p < .05$; **$p < .01$; ***$p < .001$. *n*: number of valid measurements.

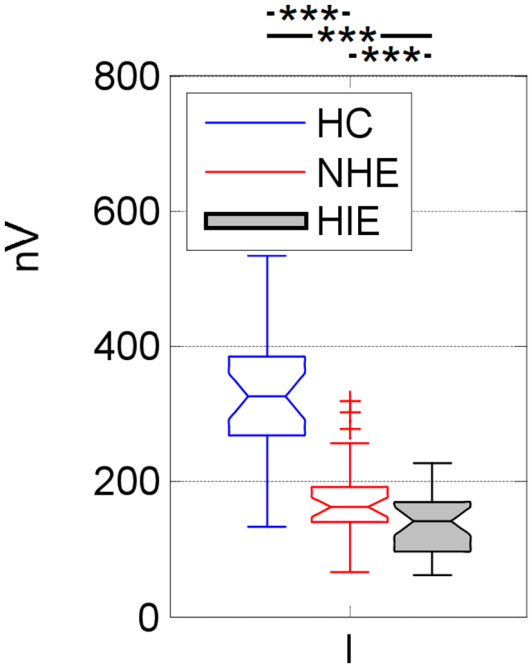


FIGURE 4 ABR wave I amplitudes. A significant decrease of the ABR amplitude for wave I was detectable between the healthy controls (HC) and the normally hearing elderly (NHE) group (ANOVA, $F_{2, 84} = 60.4$, $p < .001$; post hoc test Tukey HSD). After controlling for the age difference between the NHE and the hearing-impaired elderly (HIE) group (ANOCOVA (covariable: age), $F_{1, 55} = 4.2$, $p = .046$), a significant difference of the wave I ABR amplitude was demonstrated as well. Controlling for audibility differences between the HC and the NHE group was neither methodologically nor statistically feasible in a reliant manner due to the broadband stimulus. Results of this analysis suggest a deterioration of cochlear synaptic transmission with hearing loss and possibly with aging itself. $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$. Notches in the boxes show the 95% confidence interval. Number of valid measurements: HC: $n = 29$, NHE: $n = 30$, HIE: $n = 28$

others assume predominant effects of hearing loss and possibly superimposed age effects (Cilento et al., 2003; Hoth et al., 2010), and several studies do not separate age and hearing loss effects in detail (Abdala & Dhar, 2012; Profant et al., 2019). Heterogeneous conclusions among these studies may be partly due to inhomogeneous definitions of normal hearing ability and of DPOAE levels as well as to different sample characteristics, DPOAE algorithms, and statistics.

In contrast, there is a lack of studies using *DPOAE thresholds* as a surrogate for OHC integrity in aging and age-related hearing loss. Gates et al. (2002, 2008) did not differentiate between an age- and hearing loss-related increase in DPOAE thresholds. Ortmann and Abdala (2016) postulated alterations in DPOAE thresholds with aging, independent of age-related hearing loss. In order to avoid imprecision due to low signal-to-noise ratios, we did not directly determine DPOAE thresholds in our study. Instead, we used linear regression analysis from suprathreshold DPOAE measurements to extrapolate DPOAE thresholds for yielding more accurate results (Gorga et al., 2003; Janssen, 2009). Beside decreasing numbers of valid DPOAEs (as expected), we observed a significant increase in DPOAE thresholds with increasing hearing loss in the elderly group. At 6 and 8 kHz, the lacking significant increase between the NHE and the HIE group was possibly due to a statistically limiting small sample size in the HIE group ($n = 3$ at 6 kHz and $n = 9$ at 8 kHz). Furthermore, at these frequencies, standing waves in the ear canal can lead up to imprecision of the results (Janssen, 2009; Mrowinski & Scholz, 2011). It was not easy to decide whether the increase in DPOAE thresholds of the NHE group was solely due to aging, and not associated with hearing loss. Indeed, significantly higher DPOAE thresholds of the NHE group than of the HC group were observed when using all available raw data. However, taking into account that some individuals of the NHE group were characterized by significantly higher PTA-thresholds at 2 and 4 kHz possibly leading up to higher DPOAE thresholds in these frequencies per se, an additional

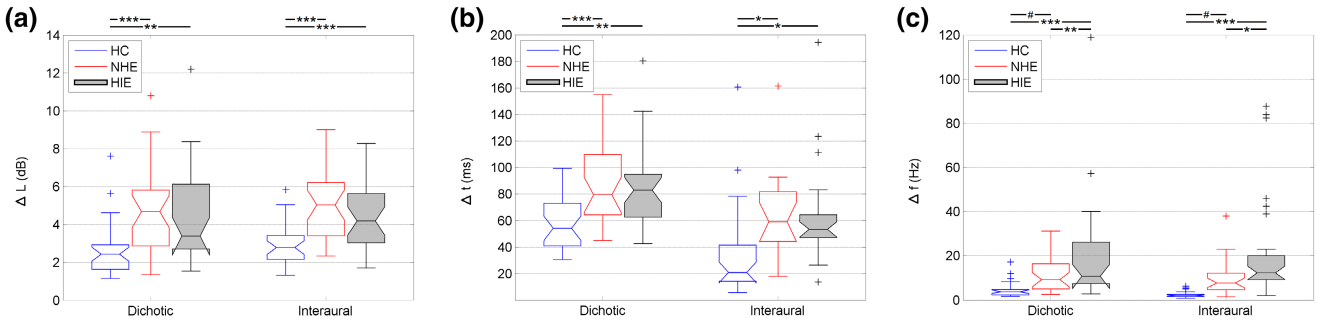


FIGURE 5 Discrimination thresholds in the CADP test battery. Just noticeable differences (JNDs) of the healthy controls (HC), the normally hearing elderly (NHE), and the hearing-impaired elderly (HIE) group for dichotic and interaural level (a), duration (b), and frequency (c) discrimination. (a,b) Level and duration discrimination performance was significantly worse in both elderly groups in comparison to the HC group but did not differ significantly between both elderly groups, suggesting aging effects independent from hearing loss. (c) Compared with the HC and the NHE group frequency discrimination ability was significantly diminished in hearing-impaired elderly subjects. The ANOVA showed a strong but nonsignificant tendency toward higher discrimination thresholds of the NHE in comparison to the HC group. This could be confirmed by an additional ANOCOVA taking in account audibility differences between these groups (covariable: average hearing loss at 6 an 8 kHz of both ears). These findings suggest a significant ARHL-associated and possibly an additional age-related deterioration in JNDs for frequency. For statistical details, please refer to Table 4. $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$; #: possibly significant. Notches in the boxes show the 95% confidence interval

**TABLE 4** Discrimination thresholds in the CADP test battery

| Group | Level discrimination dichotic | Level discrimination interaural | Duration discrimination dichotic | Duration discrimination interaural | Frequency discrimination dichotic | Frequency discrimination interaural |
|---|---|---|---|---|---|---|
| HC | 2.7 ± 1.4 dB ($n = 30$) | 2.9 ± 1.0 dB ($n = 30$) | 58.1 ± 20.0 ms ($n = 30$) | 35.1 ± 33.7 ms ($n = 30$) | 4.5 ± 3.4 Hz ($n = 30$) | 2.3 ± 1.3 Hz ($n = 30$) |
| NHE | 4.7 ± 2.3 dB ($n = 30$) | 5.1 ± 2.0 dB ($n = 30$) | 86.7 ± 30.8 ms ($n = 29$) | 64.0 ± 35.4 ms ($n = 16$) | 11.3 ± 7.4 Hz ($n = 29$) | 10.3 ± 8.0 Hz ($n = 29$) |
| HIE | 4.4 ± 2.4 dB ($n = 30$) | 4.6 ± 1.9 dB ($n = 30$) | 84.5 ± 31.4 ms ($n = 28$) | 62.5 ± 38.8 ms ($n = 22$) | 19.3 ± 23.0 Hz ($n = 29$) | 21.8 ± 23.8 Hz ($n = 30$) |
| *p*-values | *ANOVA*:<br>HC NHE: <.001***<br>HC HIE: .0077**<br>NHE HIE: .76<br>*ANOCOVA*:<br>HC NHE: .020*<br>NHE HIE: .35 | *ANOVA*:<br>HC NHE: <.001***<br>HC HIE: <.001***<br>NHE HIE: .54<br>*ANOCOVA*:<br>HC NHE: .0016*<br>NHE HIE: .19 | *ANOVA*:<br>HC NHE: <.001***<br>HC HIE: .0014**<br>NHE HIE: .95<br>*ANOCOVA*:<br>HC NHE: .009**<br>NHE HIE: .47 | *ANOVA*:<br>HC NHE: .030*<br>HC HIE: .022*<br>NHE HIE: .99<br>*ANOCOVA*:<br>HC NHE: .071<br>NHE HIE: .39 | *ANOVA*:<br>HC NHE: .16<br>HC HIE: <.001***<br>NHE HIE: .078<br>*ANOCOVA*:<br>HC NHE: .027*<br>NHE HIE: .0091** | *ANOVA*:<br>HC NHE: .096<br>HC HIE: <.001***<br>NHE HIE: .009**<br>*ANOCOVA*:<br>HC NHE: .0036**<br>NHE HIE: .011* |

*Note*: Mean ± *SD* and *p*-values for each group-wise comparison. A significant deterioration of average JNDs could be detected between the healthy controls (HC) and both elderly (normally hearing elderly—NHE and hearing-impaired elderly—HIE) groups but not between the elderly groups for dichotic and interaural level and duration discrimination tasks, suggesting an aging effect on performance (ANOVA, $F_{2, 87} = 8.1$, $p < .001$ (dichotic level discrimination)/$F_{2, 87} = 13.5$, $p < .001$ (interaural level discrimination)/$F_{2, 84} = 9.7$, $p < .001$ (dichotic duration discrimination)/$F_{2, 65} = 5.1$, $p < .01$ (interaural duration discrimination); post hoc test Tukey HSD). These results could be confirmed after controlling for the age difference between NHE and HIE (ANOCOVA, $F_{1, 57} = .87$, $p = .35$ (dichotic level discrimination)/$F_{1, 57} = 1.8$, $p = .19$ (interaural level discrimination)/$F_{1, 54} = .53$, $p = .47$ (dichotic duration discrimination)/$F_{1, 35} = .76$, $p = .39$ (interaural duration discrimination)) and, with the exception of interaural duration discrimination, after controlling for high-frequency hearing loss between HC and NHE (ANOCOVA, covariable: average hearing loss at 6 an 8 kHz of both ears, $F_{1, 57} = 5.7$, $p = .020$ (dichotic level discrimination)/$F_{1, 57} = 11.0$, $p = .0016$ (interaural level discrimination)/$F_{1, 56} = 7.4$, $p = .009$ (dichotic duration discrimination)/$F_{1, 43} = 3.4$, $p = .071$ (interaural duration discrimination)). For dichotic and interaural frequency discrimination tasks, statistical analyses showed a significant increase of the JNDs of the HIE group in comparison to both other groups, proving an age-related hearing loss effect on JNDs (ANOVA, $F_{2, 85} = 8.3$, $p < .001$ (dichotic frequency discrimination)/$F_{2, 86} = 13.5$, $p < .001$ (interaural frequency discrimination); post hoc test Tukey HSD. Additional ANOCOVA controlling for age difference between NHE and HIE, $F_{1, 55} = 7.3$, $p < .01$ (dichotic frequency discrimination)/$F_{1, 56} = 6.8$, $p = .011$ (interaural frequency discrimination)). A tendency toward increasing JNDs between the HC and the NHEgroup, suggesting aging effects, could be confirmed after controlling for high-frequency hearing loss (ANOCOVA, covariable: average hearing loss at 6 an 8 kHz of both ears, $F_{1, 56} = 5.1$, $p = .027$ (dichotic frequency discrimination)/$F_{1, 56} = 9.2$, $p = .0036$ (interaural frequency discrimination). *$p < .05$; **$p < .01$; ***$p < .001$. *n*: number of valid measurements.

analysis of a special NHE subgroup with comparable PTA-thresholds to the HC group could not show significant differences in DPOAE thresholds anymore. It therefore remained unclear whether this lack of significance is due to physiological (no changes in DPOAE thresholds solely with increasing age) or statistical (NHE15dB sample size too small) effects. For 6 and 8 kHz, the special ANOCOVA controlling for audibility effects still detected significant aging effects, but upper mentioned standing wave problems have to be taken in account as well. Correlation analysis, on the other hand, showed significant and high correlations of DPOAE thresholds both with age and (only slightly higher) with hearing loss. In summary, we assume a hearing loss-associated increase in DPOAE thresholds, whereas a pure aging effect on thresholds remains unclear (but seems possible).

From a *physiological* point of view, DPOAE thresholds represent the lowest stimulus level to elicit a measurable contraction of outer hair cells. In contrast DPOAE levels correlate with the suprathreshold efficacy of the nonlinear cochlear amplifier. Taking the results of both our study and upper mentioned studies into consideration, increasing age-related hearing loss and possibly aging per se seem to trigger dysfunction of OHCs in multiple dimensions: Not only a higher stimulus level is required to yield an active contraction of OHCs (shown by rising DPOAE thresholds), but also the efficacy of the suprathreshold nonlinear cochlear amplifier deteriorates (represented by decreasing DPOAE levels). From a *pathophysiological and anatomical* view, these changes are most likely due to a decrease in the number of intact OHCs (Nelson & Hinojosa, 2006; Schuknecht & Gacek, 1993; Ueberfuhr et al., 2016), which seem to be particularly vulnerable to cumulative vascular, toxic, and noise damaging with aging (M. P. Gorga et al., 2005; Nakashima et al., 1995; Shi, 2011; Suzuki et al., 1998; Tadros et al., 2005; Uchida et al., 2008). It has to be taken into account, however, that DPOAE thresholds and amplitudes may depend on further factors, for example transmission characteristics of the middle ear and the outer ear canal (Abdala & Dhar, 2012) and activity of the inhibiting medial olivocochlear system (Boothalingam et al., 2014). The first were assessed indirectly by otoscopy and tympanometry in our study, the latter could not be quantified.

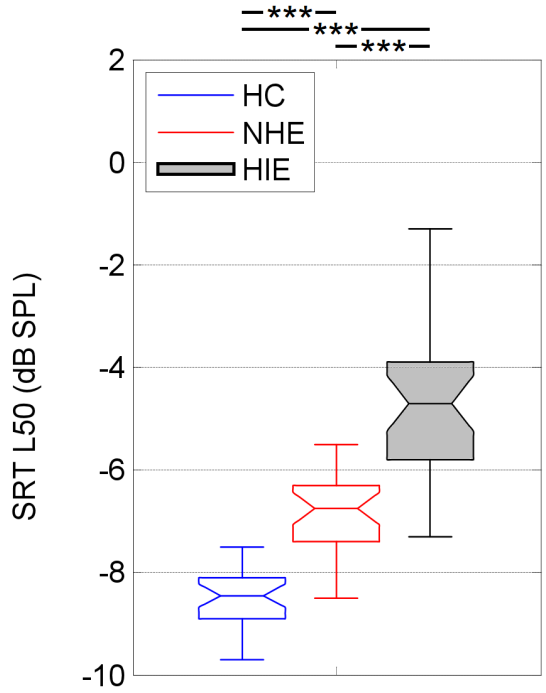


**FIGURE 6** Speech understanding in noise in the OLSA. The SRT $L_{50}$ (speech reception threshold for 50% intelligibility) differed significantly between the healthy controls (HC), the normally hearing elderly (NHE), and the hearing-impaired elderly (HIE) group (ANOVA, $F_{2, 87} = 103.1$, $p < .001$; post hoc test Tukey HSD). Also, after controlling for the differences in high-frequency hearing loss between HC and NHE and a slight age difference between NHE and HIE by means of an ANOCOVA, the same results were detectable (ANOCOVA (covariable: age), $F_{1, 57} = 32.1$, $p < .001$; ANOCOVA (covariable: average hearing loss at 6 an 8 kHz of both ears), $F_{1, 57} = 33.1$, $p < .001$). *$p < .05$; **$p < .01$; ***$p < .001$. Number of valid measurements: HC: $n = 30$, NHE: $n = 30$, HIE: $n = 30$

## 4.2 | Signal transmission in the auditory nerve and brainstem—ABR

ABR *interpeak latencies* correlate with signal transmission times in the auditory nerve (N. VIII) and brainstem: IPL I–III represents the signal transmission time from the distal part of the auditory nerve to the cochlear nucleus in the lower pons, IPL III–V from the cochlear nucleus to the lateral lemniscus and IPL I–V (the so called central transmission time) subsumes both sections (Legatt, 2012).

In our study, a significantly prolonged central transmission time in both elderly groups in comparison to the HC group was revealed by a significant increase in IPL III–V, whereas IPL I–III did not change significantly with age or with age-related hearing loss. Significant differences between the two elderly groups were not observed in IPL I–III and IPL III–V. IPL I–III is mainly determined by signal transmission time in the auditory nerve, which strongly depends on the integrity of its saltatory signal conduction and its myelin sheaths maintained by Schwann cells and oligodendrocytes (Klinke et al., 2005; Legatt, 2012; Wang et al., 2009). Neither aging nor age-related hearing loss seem to result in severe demyelination or relevant changes in signal transduction in the auditory nerve. In contrast, prolonged IPLs III-V in both elderly groups indicate alterations in brainstem auditory signal processing with increasing age, but not with age-related hearing loss. Possible mechanisms for these changes comprise (1) alterations in brainstem auditory fibers and synaptic transmission, as shown in animal models (Frisina & Walton, 2006; Jayakody et al., 2018; Lee, 2013); (2) alterations in homeostasis and effect of fibroblast growth factor (FGF), resulting in impaired myelination of brainstem auditory tracts (Wang et al., 2009); and (3) a loss of neuropil of the cochlear nucleus, correlating with compromised interneuronal connections and auditory processing (Hinojosa & Nelson, 2011).

Results of previous studies concerning ABR-IPLs in ARHL are quite heterogeneous: Some postulate significant effects of aging (increases or decreases, e.g., Chu, 1985; Costa et al., 1990; Elberling &

Parbo, 1987; Oku & Hasegewa, 1997; Rosenhall et al., 1985), some negate IPL-changes with aging (e.g., Burkard & Sims, 2001; Harkins, 1981; Konrad-Martin et al., 2012; Martini et al., 1991; Prosser & Rosignoli, 1992) and some assign observed IPL-changes to age-related hearing loss rather than to aging itself (e.g., Boettcher, 2002; Burkard & Sims, 2001; Harkins, 1981; Ottaviani et al., 1991). High-frequency hearing loss in the NHE group could be a confounder of the IPL results in our study as well and impeded a straightforward distinction of aging-related vs. hearing loss-related effects, as stimulus intensity was identical for all groups. Absolute ABR-latencies are well known to be delayed in hearing-impaired subjects (Lehnhardt & Laszig, 2009). Interpeak latencies, in contrast, should be essentially independent of peripheral hearing capability, as all waves are expected to be equally delayed by hearing loss. The influence of peripheral hearing loss on NHE IPL results could not be excluded a priori and their interpretation had to be done with special caution. Nevertheless, the present study mainly assumes aging and not hearing loss dependent effects on IPL III–V (and consequently on IPL I–V) due to the following reasons: (1) Hearing loss does not seem to influence IPL III–V in our study, as the IPL III–V results of the NHE and the HIE group are identical. We therefore did not try to eliminate differences in audibility between HC and NHE by additional statistical analyses. (2) IPLs in previous studies tended to be shorter in cochlear hearing loss (e.g., Burkard & Sims, 2001; Elberling & Parbo, 1987; Fowler & Noffsinger, 1983; Legatt, 2012), which is in contrast to the prolongation of IPLs observed in our study, and (3) the interaural CADP results for stimulus level and stimulus duration discrimination, which also reflect integrity of brainstem auditory processing, showed alterations with aging and not with age-related hearing loss, as well (see Section 4.3). An analogous compensation for peripheral hearing loss—as it was done in the CADP tests by presenting the stimulus at a fixed sensation level dependent on audibility—was not feasible in the ABR testing due to the broadband nature of the stimulus.

ABR *wave I amplitude* registers the synchronized action potentials in the proximal auditory nerve and reflects synaptic transmission between cochlear hair cells and the auditory nerve fibers (Lehnhardt & Laszig, 2009). Previous studies assumed that decreased ABR wave I amplitude could be a surrogate of cochlear synaptopathy, which clinically results in difficulty understanding speech in noise (Barbee et al., 2018; Kujawa & Liberman, 2015; Liberman & Kujawa, 2017; Sergeyenko et al., 2013). Our study detected a significant decrease in ABR wave I amplitude with age-related hearing loss. A significantly diminished ABR wave I amplitude between the HC and the NHE group could either reflect aging effects or differences in high-frequency audibility, as stimulus intensity was identical for all groups. Results of the NHE group therefore have to be interpreted with special caution with respect to aging effects. Controlling for audibility statistically was not really feasible because of the broadband nature of the click stimulus. Out of interest we nevertheless conducted an ANOCOVA controlling for high-frequency hearing loss and still showing a significant difference between the ABR wave I amplitude of the HC and the NHE group (covariable: average hearing loss at 4, 6, and 8 kHz of both ears, i.e., the frequencies differing highly significant between the HC and the NHE group, $F_{1, 56} = 28.4$, $p < .001$). Altogether results suggest cochlear synaptopathy in age-related hearing loss; additional aging effects on cochlear synaptic transmission seem possible but could not be proven.

### 4.3 | Central auditory discrimination performance

In a review of evidence for central ARHL (that means an age-related central auditory processing deficit independent of cognitive decline and peripheral hearing loss), Humes et al. (2012) emphasized three requirements of selective central auditory tests: compensation for peripheral hearing loss, a low cognitive load, and the use of nonspeech stimuli. The CADP test battery of our study is able to fulfill all three conditions by presenting nonspeech stimuli at a hearing threshold-adapted level and by using a uniform and easy feedback method for all subtests, thereby minimizing a possible cognitive load. Low correlations between CADP test results and 1 kHz-PTA-thresholds prove independence of the CADP from peripheral hearing impairment. An additional ANOCOVA (covariable: average hearing loss at 6 and 8 kHz of both ears) ruled out interfering high-frequency hearing loss effects on the results.

As described in 2.7 interaural tests assess integrity of brainstem auditory processing and are not influenced by di- and telencephalic lesions. Under physiological conditions, interaural time differences (ITDs) and interaural level differences (ILDs) are used—besides spectral cues—for sound localization in the horizontal plane. They are initially extracted by the medial and lateral superior olive, respectively, and conducted via the lateral lemniscus to the inferior colliculus (Grothe et al., 2010; Middlebrooks, 2015; Pickles, 2015; Salminen et al., 2015). According to the results of the interaural duration and level discrimination in our test battery discrimination performance of the mentioned brainstem structures deteriorates with aging, but not with increasing age-related hearing loss. This is consistent with conclusions of other studies (Dobreva et al., 2011; Fitzgibbons & Gordon-Salant, 2010; Freigang et al., 2014; Freigang et al., 2015) as well as with results of the test-developers (Bungert-Kahl et al., 2004), whereby the latter did not really differentiate between age-related and hearing status-related effects. In contrast, the interaural frequency discrimination tests imitate a horizontal movement of a sound source by means of a continuous phase shift between both ears. So far, a specific brainstem structure responsible for horizontal motion detection is not known (Kuwada et al., 1979; Middlebrooks, 2015). Our results suggest poorer horizontal motion detection performance with age and demonstrate a significant deterioration with age-related hearing loss. Other studies using comparable interaural frequency tests are difficult to interpret: For example, Bungert-Kahl et al. (2004) once again observe higher difference limens in elderly subjects but do not separate age- and hearing loss-related phenomena. Freigang et al. (2011) postulate an age-related deterioration without hearing loss-associated effects, but, in fact, only rely on compensation of hearing loss by adapted stimulus levels (analogous to our algorithm) and do not evaluate results of different grades of hearing loss.

Dichotic tests, on the contrary, specifically assess contralateral di- and telencephalic discrimination performance independent of brainstem integrity (see Section 2.7). Physiologically, auditory signal duration is encoded in the central nervous system by the duration of neural firing and by specific on- and off-answers at the beginning and the end of the stimulus (Freigang et al., 2011; Neumann & Rübsamen, 2005). Level is encoded by the firing rate of neural fibers and by the range of activated fibers in the auditory nerve or the central nervous system (Neumann & Rübsamen, 2005; Schreiner & Malone, 2015). Until now, it is not clear where signal duration and level are represented in cortical areas. In contrast, there is a clear tonotopic organization at all levels of the auditory system from the cochlea to the auditory cortices, which, in addition to neural firing periodicity, provides information about stimulus frequency (Hackett, 2015; Klinke et al., 2005; Leaver & Rauschecker, 2016; Pickles, 2015). In order to compare the signals of the triplet and to find the deviant test signal in the CADP test, a temporary storage of all three signals in the sensory register of the auditory cortex is necessary (Ludwig, 2009). Analogously to the interaural mode, our dichotic duration and level discrimination tests gave proof of significantly declining performance of the involved di- and telencephalic structures with increasing age, but not with age-related hearing loss. The dichotic frequency discrimination test could show a possibly significant trend toward worse discrimination performance with increasing age and a significant deterioration with age-related hearing loss. Apparently the di- and telencephalic tonotopic structural organization is impaired by age-related hearing loss and possibly by aging alone. Previous studies concerned with comparable central discrimination tasks show, once again, heterogeneous results: Bertoli et al. (2002), He et al. (1998) and Humes et al. (2010) postulated an age-related deterioration of temporal discrimination performance, as tested by gap detection procedures in normally hearing or audiogram-matched elderly or by using spectrally shaped stimuli, respectively. Additionally, Gallun et al. (2014) found effects of hearing loss on gap detection thresholds, which, in contrast, were denied by Ozmeral et al. (2016). Bungert-Kahl et al. (2004) described higher difference limens in elderly in dichotic duration, level, and frequency discrimination tasks without separating age- and hearing loss dependent phenomena. Similar to our results, Freigang et al. (2011) observed impaired dichotic frequency discrimination with aging and increasing age-related hearing loss. In summary, most of the upper mentioned studies agree on an age-related deterioration of central discrimination performance despite different test procedures. Additional effects of age-related hearing loss (as found in the dichotic frequency discrimination in our study) remain controversial, however. Generally, it has to be taken into account that absolute results of CADP tests are dependent on stimulus presentation, for example stimulus length and repetition rate (Kuroda et al., 2013).

Pathophysiologically, the following underlying mechanisms can be discussed: (1) *Macroscopic alterations in the central auditory nervous system*: In some studies MRI morphometry showed an age-related atrophy of the auditory cortex that exceeded general age-related brain atrophy and was independent of peripheral hearing capability (Ouda et al., 2015; Profant et al., 2014). Another study, however, postulated an association of auditory cortex volume with age-related hearing loss (Eckert et al., 2012). These phenomena could be partly due to a (2) *decrease in central neuron populations*: *N*-acetylaspartate concentration, which indirectly assesses neuronal integrity, decreases with aging independently of age-related hearing loss, as shown by MR-spectroscopy. This suggests an age-dependent decline in central auditory neuron populations (Profant et al., 2013) (3) *Alterations in metabolism and signal transmission*: An increase in lactate levels in the auditory cortex could be due to an age- and age-related hearing loss dependent mitochondrial dysfunction (Profant et al., 2013). Synaptic transmission showed an age-related lack of (mainly Glycine- and GABA-mediated) synaptic inhibition in animal and human experiments, which possibly results in altered central noise canceling ability (Caspary et al., 2008; Jayakody et al., 2018; Profant et al., 2013). Structural integrity of subcortical auditory nerve fibers could be impaired in aging (Cardin, 2016; Lutz et al., 2007; Profant et al., 2014). (4) *Functional reorganization*: Activation patterns in the auditory cortices and frontal cortex areas change with aging and age-related hearing loss (Billings et al., 2012; Cardin, 2016; Profant et al., 2015), which could lead up to a deterioration in central auditory signal processing.

In summary, results of our CADP test battery proved differential aging of various parts and functional aspects of the central auditory system. They, in general, provided further evidence for an independent central ARHL component not solely related to peripheral hearing loss, as recently postulated by Bao et al. (2020). The more pronounced peripheral hearing loss in the NHE group compared with the HC group made it difficult to attribute the poorer central discrimination performance of the NHE group to aging alone. The effects of peripheral hearing loss on central discrimination performance cannot be ruled out definitely. Nevertheless, the lack of significant differences in most discrimination tasks between the two elderly groups (with their significantly differing peripheral hearing loss) suggests that aging itself is a relevant and independent factor for deterioration of central auditory performance.

### 4.4 | Speech in noise—OLSA

Speech understanding in noise, as measured by the OLSA in our test battery, significantly deteriorated in both elderly groups compared to the HC group and, as expected, was significantly worse in the HIE group than in the NHE group. Until now no clear topodiagnostic specificity is known for the OLSA. In fact, results are expected to be determined by (1) peripheral, especially high-frequency hearing loss (George et al., 2007); (2) impaired OHC function, as shown above, which results in reduced cochlear sensitivity and frequency selectivity and consecutive difficulty in extracting the speech- from the noise signal (Janssen & Müller, 2008; Johannesen et al., 2016); (3) cochlear synaptopathy (reflected in decreasing ABR wave I amplitudes in our study), which affects mainly high-threshold nerve fibers and plays an important role for altered transduction of

TABLE 5 Summary of results

| | DPOAE threshold | ABR wave I amplitude | ABR: IPL I-III | ABR: IPL III-V | CADP: Interaural LD/DD-threshold | CADP: Interaural FD-threshold | CADP: Dichotic LD/DD-threshold | CADP: Dichotic FD-threshold | OLSA: SRT $L_{50}$ |
|---|---|---|---|---|---|---|---|---|---|
| Effect of aging | ? (increase?) | ? (decrease?) | – | + (increase) | + (increase) | ? (increase?) | + (increase) | ? (increase?) | +? (deterioration) |
| Effect of age-related hearing loss | + (increase) | + (decrease) | – | – | – | + (increase) | – | + (increase) | + (deterioration) |
| Represented structure/functional aspect | OHC | Cochlear synaptic transmission | N. VIIII to cochlear nucleus: Myelin-sheath | Brainstem: Signal transduction from cochlear nucleus to lateral lemniscus | Brainstem (LSO/MSO, lateral lemniscus, inferior colliculus): Localization ability in horizontal plane | Brainstem (structural correlate unclear): Motion detection in horizontal plane | Di–/ Telencephalic level/duration discrimination (structural correlate unclear) | Di–/Telencephalon: Tonotopic organization | Speech-understanding in noise (structural correlate unclear) |

*Note*: Effects of aging and age-related hearing loss are attributed to topographical structures or functional aspects (as far as known). +: statistically significant effect; +?: statistically significant, but clinically questionable effect; –: no statistically significant effect; ?: unclear. LD/DD/FD: Level/Duration/Frequency discrimination in the CADP test battery.

the suprathreshold speech signal to the central nervous system (Kujawa & Liberman, 2015; Liberman & Kujawa, 2017; Sergeyenko et al., 2013; Tawfik et al., 2020); (4) impaired auditory transduction in the brainstem, as shown by our ABR interpeak latency results; and (5) deterioration of central auditory processing, as shown by our CADP results. Due to this mixture of phenomena, it is not easy to decide whether aging per se affects the OLSA results of our NHE group. We rather expect a mixture of aging- and age-related hearing loss effects. Nevertheless, and despite its missing topodiagnostic specificity, the OLSA can be considered as a kind of a summarizing test in our battery, as it shows the overall results of all observed phenomena and as it conveys an important impression of the participants' everyday functioning, which is strongly influenced by speech understanding in competing noise. Even the best hearing quartile of a western elderly society has to be expected to suffer from significantly diminished speech understanding in noise in comparison to young individuals.

## 5 | CONCLUSION

In conclusion our study provides further evidence for a multifocal aging process of the auditory system. All parts of the auditory pathway examined in the study show ARHL-related deteriorations in performance, associated partly with aging and partly with age-related hearing loss, whereby some overlap cannot be ultimately excluded. An independent central ARHL component due to aging itself (and not only attributable to peripheral hearing loss) is supported by the results of our CADP test. Table 5 provides a summarizing overview of our results and tries a topodiagnostic correlation, as discussed above. Aging itself results in a significant deterioration of brainstem signal transmission and certain aspects of central sound processing including speech understanding in noise; possible additional changes comprise impaired OHC function and cochlear synaptopathy. Age-related hearing loss leads up to an additional significant deterioration of OHC and cochlear synaptic function, of motion detection in the horizontal plane, of speech understanding in noise and to impairment of the central tonotopic organization. The altered auditory performance results in a significant subjective hearing handicap, as shown by the HHIE-S.

A main strength of our study lies in the assessment of each individual's whole auditory system by means of an extensive test battery. This enabled inter- and intraindividual correlations and is in contrast to many previous studies focusing on single functional aspects, like gap detection performance. An unintended age difference between the NHE and the HIE group and a slight, but significant high-frequency hearing loss in the NHE group impeded strict separation between pure age effects and hearing loss-associated effects and were mainly due to the difficulty in recruiting a sufficient number of normally hearing elderly, especially at high frequencies. This has been a common problem in comparable studies. We tried to compensate for these group differences methodically and statistically. Nevertheless, some effects of peripheral hearing status on the

results of the NHE group cannot be definitely ruled out—this main limitation is essentially relevant for the interpretation of the DPOAE thresholds and the ABR wave I amplitude, and also for the evaluation of an independent aging-related central ARHL component (see the respective sections of the Discussion). Both elderly groups showed certain degrees of peripheral, mainly high-frequency hearing loss. The NHE group—despite being classified as normally hearing by WHO criteria—was not characterized by flat audiograms over the whole frequency range as shown by the HC group. The NHE HIE group comparison therefore rather evaluated hearing performance of elderly with minimally vs. relevantly impaired peripheral hearing. Even so one has to bear in mind that the NHE group mainly represents the best-hearing quartile of an average elderly population and results are clinically representative for normally hearing elderly in a general non-study context.

For future studies, a multicenter concept should be considered in order to ease the recruitment of normally hearing elderly. No clear hints of gender-related differences were seen in our sample; nevertheless, future large-scale studies should also focus on gender-specific aging aspects in the auditory system. In contrast to our cross-sectional concept, longitudinal trials could show the intraindividual dynamics of the observed processes.

Some methodological limitations of our study need to be addressed: First, we could not perform an exact power analysis in advance due to missing standardized data for our CADP test. This could result in sample sizes insufficient to discover true significant effects (e.g., in the CAPD and DPOAE tests). On the other hand, an inadequate sample size can pretend significant results which—in reality—are not highly robust. For future studies, power analyses based on the data of this study should be performed in advance. Second, noise and ototoxic exposure could not be quantified exactly in the retrospective short history taken by the Questionnaire for auditory tests. Confounding moderate noise and ototoxic exposure could affect hearing performance additionally and independently from aging and ARHL effects. Third, we did not assess extensive high-frequency hearing loss (above 8 kHz) which seems to be a sign of early ARHL and can be associated with "hidden hearing loss," that means impaired speech understanding in noise despite regular PTA-thresholds (Barbee et al., 2018; Peñaranda et al., 2021; Sun et al., 2021). Possibly some of our healthy controls already exhibit some degree of extensive high-frequency hearing loss not consistent with totally normal hearing. Generally, we had to find a compromise between a reasonable and thorough test battery and a feasible and acceptable time expenditure for the participants. In some test procedures, this can lead to reduced coverage of interesting cofactors and data that could have been collected in a single-test study—a common drawback of multitest studies. Last but not least, our study cannot etiologically clarify the interindividually varying propensity to ARHL.

Nowadays standard therapy of ARHL is limited to compensation for peripheral hearing loss by amplification techniques. The multifocal ARHL-related phenomena proven in our study address the need for a broader and multimodal ARHL-therapy, that not only compensates peripheral hearing loss, but also considers neurodegenerative and central aspects of auditory aging, for example by special auditory training and neuroprotective agents. Further large-scale studies are needed both in order to reevaluate the findings of our study and to assess the success of a multimodal therapeutic concept.

## AUTHOR CONTRIBUTIONS

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Conceptualization*, D.P., V.S., and T.J.; *Methodology*, D.P., V.S., and T.J.; *Software*, V.S.; *Validation*, D.P. and V.S.; *Investigation*, D.P. and V.S.; *Formal Analysis*, D.P. and V.S.; *Resources*, D.P., V.S., and T.J.; *Data Curation*, D.P. and V.S.; *Writing – Original Draft*, D.P., V.S., and T.J.; *Writing – Review and Editing*, D.P., V.S., and T.J.; *Visualization*, D.P. and V.S.; *Supervision*, V.S. and T.J.; *Project Administration*, D.P.; *Funding acquisition*, V.S. and T.J.

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## CONFLICT OF INTEREST

Dominik Pürner: None. Volker Schirkonyer: Currently employee of PATH MEDICAL GmbH, Germering, Germany. Thomas Janssen: None.

## DECLARATION OF TRANSPARENCY

The authors, reviewers and editors affirm that in accordance to the policies set by the *Journal of Neuroscience Research*, this manuscript presents an accurate and transparent account of the study being reported and that all critical details describing the methods and results are present.

## PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1002/jnr.25068.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on reasonable request from the corresponding author. Main raw data are provided in the Supporting Information Table.

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## REFERENCES


Abdala, C., & Dhar, S. (2012). Maturation and aging of the human cochlea: a view through the DPOAE looking glass. *Journal of the Association for Research in Otolaryngology*, *13*(3), 403–421. https://doi.org/10.1007/s10162-012-0319-2

American Speech-Language-Hearing-Association. (1997). *Guidelines for audiologic screening*. www.asha.org/policy

American Speech-Language-Hearing-Association. (2016). *Adult hearing screening*. http://www.asha.org/PRPSpecificTopic.aspx?folderid=8589942721&section=Key_Issues

Bao, J., Yu, Y., Li, H., Hawks, J., Szatkowski, G., Dade, B., Wang, H., Liu, P., Brutnell, T., Spehar, B., & Tye-Murray, N. (2020). Evidence for independent peripheral and central age-related hearing impairment. *Journal of Neuroscience Research*, *98*(9), 1800–1814. https://doi.org/10.1002/jnr.24639

Barbee, C. M., James, J. A., Park, J. H., Smith, E. M., Johnson, C. E., Clifton, S., & Danhauer, J. L. (2018). Effectiveness of auditory measures for detecting hidden hearing loss and/or cochlear synaptopathy: A systematic review. *Seminars in Hearing*, *39*(2), 172–209. https://doi.org/10.1055/s-0038-1641743

Bertoli, S., Probst, R., & Jordan, P. (1996). Das Hörhandicap—Eine Ergänzung zum audiometrischen Hörverlust. Ergebnisse einer explorativen Studie über auditive Kommunikationsstörungen im Alter. *HNO*, *44*(7), 376–384.

Bertoli, S., Smurzynski, J., & Probst, R. (2002). Temporal resolution in young and elderly subjects as measured by mismatch negativity and a psychoacoustic gap detection task. *Clinical Neurophysiology*, *113*(3), 396–406.

Biedermann, F., Bungert, P., Dorrscheidt, G. J., von Cramon, D. Y., & Rubsamen, R. (2008). Central auditory impairment in unilateral diencephalic and telencephalic lesions. *Audiology & Neuro-Otology*, *13*(2), 123–144. https://doi.org/10.1159/000111784

Billings, C., Tremblay, K., & Willot, J. (2012). The aging auditory system. In R. F. Burkard & K. Tremblay (Eds.), *Translational perspectives in auditory neuroscience* (pp. 63–82). Plural Publishing Inc.

Boege, P., & Janssen, T. (2002). Pure-tone threshold estimation from extrapolated distortion product otoacoustic emission I/O-functions in normal and cochlear hearing loss ears. *Journal of the Acoustical Society of America*, *111*(4), 1810–1818. https://doi.org/10.1121/1.1460923

Boettcher, F. A. (2002). Presbyacusis and the auditory brainstem response. *Journal of Speech, Language, and Hearing Research*, *45*(6), 1249–1261.

Boothalingam, S., Purcell, D., & Scollie, S. (2014). Influence of 100Hz amplitude modulation on the human medial olivocochlear reflex. *Neuroscience Letters*, *580*, 56–61. https://doi.org/10.1016/j.neulet.2014.07.048

Bungert-Kahl, P., Biedermann, F., Dörrscheidt, G. J., von Cramon, D. Y., & Rübsamen, R. (2004). Psychoacoustic test tools for the detection of deficits in central auditory processing: Normative data. *Zeitschrift fur Audiologie*, *43*(2), 48–71.

Burkard, R. F., & Sims, D. (2001). The human auditory brainstem response to high click rates: aging effects. *American Journal of Audiology*, *10*(2), 53–61.

Cardin, V. (2016). Effects of aging and adult-onset hearing loss on cortical auditory regions. *Frontiers in Neuroscience*, *10*, 199. https://doi.org/10.3389/fnins.2016.00199

Caspary, D. M., Ling, L., Turner, J. G., & Hughes, L. F. (2008). Inhibitory neurotransmission, plasticity and aging in the mammalian central auditory system. *The Journal of Experimental Biology*, *211*(Pt 11), 1781–1791. https://doi.org/10.1242/jeb.013581

Chu, N. S. (1985). Age-related latency changes in the brain-stem auditory evoked potentials. *Electroencephalography and Clinical Neurophysiology*, *62*(6), 431–436.

Cilento, B. W., Norton, S. J., & Gates, G. A. (2003). The effects of aging and hearing loss on distortion product otoacoustic emissions. *Otolaryngology and Head and Neck Surgery*, *129*(4), 382–389. https://doi.org/10.1016/s0194-59980300637-5

Costa, P., Benna, P., Bianco, C., Ferrero, P., & Bergamasco, B. (1990). Aging effects on brainstem auditory evoked potentials. *Electromyography and Clinical Neurophysiology*, *30*(8), 495–500.

DIN Deutsches Institut für Normung e.V. (2002). *DIN EN 60645-1:2002-09, Akustik—Audiometer—Teil 1: Reinton-Audiometer (IEC 60645-1:2001)*. Beuth Verlag GmbH.

DIN Deutsches Institut für Normung e.V. (2009). *DIN EN ISO 389-9:2009-12, Akustik—Standard-Bezugspegel für die Kalibrierung audiometrischer Geräte—Teil 9: Vorzugs-Messbedingungen zur Bestimmung von Bezugs-Hörschwellenpegeln (ISO 389-9:2009)*. Beuth Verlag GmbH.

DIN Deutsches Institut für Normung e.V. (2011). *DIN EN ISO 8253-1:2011-04, Akustik—Audiometrische Prüfverfahren—Teil 1: Grundlegende Verfahren der Luft- und Knochenleitungs-Schwellenaudiometrie mit reinen Tönen (ISO 8253-1:2010)*. Beuth Verlag GmbH.

DIN Deutsches Institut für Normung e.V. (2017). *DIN EN ISO 7029:2017-06 Akustik—Statistische Verteilung von Hörschwellen in Bezug auf das Alter und das Geschlecht (ISO 7029:2017)*. Beuth Verlag GmbH.

Dobreva, M. S., O'Neill, W. E., & Paige, G. D. (2011). Influence of aging on human sound localization. *Journal of Neurophysiology*, *105*(5), 2471–2486. https://doi.org/10.1152/jn.00951.2010

Eckert, M. A., Cute, S. L., Vaden, K. I., Jr., Kuchinsky, S. E., & Dubno, J. R. (2012). Auditory cortex signs of age-related hearing loss. *Journal of the Association for Research in Otolaryngology*, *13*(5), 703–713. https://doi.org/10.1007/s10162-012-0332-5

Elberling, C., & Parbo, J. (1987). Reference data for ABRs in retrocochlear diagnosis. *Scandinavian Audiology*, *16*(1), 49–55.

Fischer, N., Weber, B., & Riechelmann, H. (2016). Presbyakusis—Altersschwerhörigkeit. [Presbycusis—Age Related Hearing Loss]. *Laryngo-Rhino-Otologie*, *95*(07), 497–510. https://doi.org/10.1055/s-0042-106918

Fitzgibbons, P. J., & Gordon-Salant, S. (2010). Age-related differences in discrimination of temporal intervals in accented tone sequences. *Hearing Research*, *264*(1–2), 41–47. https://doi.org/10.1016/j.heares.2009.11.008

Fowler, C. G., & Noffsinger, D. (1983). Effects of stimulus repetition rate and frequency on the auditory brainstem response in normal cochlear-impaired, and VIII nerve/brainstem-impaired subjects. *Journal of Speech and Hearing Research*, *26*(4), 560–567.

Freigang, C., Richter, N., Rubsamen, R., & Ludwig, A. A. (2015). Age-related changes in sound localisation ability. *Cell and Tissue Research*, *361*(1), 371–386. https://doi.org/10.1007/s00441-015-2230-8

Freigang, C., Schmidt, L., Wagner, J., Eckardt, R., Steinhagen-Thiessen, E., Ernst, A., & Rubsamen, R. (2011). Evaluation of central auditory discrimination abilities in older adults. *Frontiers in Aging Neuroscience*, *3*, 6. https://doi.org/10.3389/fnagi.2011.00006

Freigang, C., Schmiedchen, K., Nitsche, I., & Rubsamen, R. (2014). Free-field study on auditory localization and discrimination performance in older adults. *Experimental Brain Research*, *232*(4), 1157–1172. https://doi.org/10.1007/s00221-014-3825-0

Frisina, R. D., & Walton, J. P. (2006). Age-related structural and functional changes in the cochlear nucleus. *Hearing Research*, *216-217*, 216–223. https://doi.org/10.1016/j.heares.2006.02.003

Gallun, F. J., McMillan, G. P., Molis, M. R., Kampel, S. D., Dann, S. M., & Konrad-Martin, D. L. (2014). Relating age and hearing loss to monaural, bilateral, and binaural temporal sensitivity. *Frontiers in Neuroscience*, *8*, 172. https://doi.org/10.3389/fnins.2014.00172

Gates, G. A., Feeney, M. P., & Mills, D. (2008). Cross-sectional age-changes of hearing in the elderly. *Ear and Hearing*, *29*(6), 865–874.

Gates, G. A., Mills, D., Nam, B. H., D'Agostino, R., & Rubel, E. W. (2002). Effects of age on the distortion product otoacoustic emission growth functions. *Hearing Research*, *163*(1–2), 53–60.

Gates, G. A., & Mills, J. H. (2005). Presbycusis. *Lancet*, *366*(9491), 1111–1120. https://doi.org/10.1016/s0140-6736(05)67423-5

George, E. L., Zekveld, A. A., Kramer, S. E., Goverts, S. T., Festen, J. M., & Houtgast, T. (2007). Auditory and nonauditory factors affecting speech reception in noise by older listeners. *The Journal of the Acoustical Society of America*, *121*(4), 2362–2375.

Gorga, M. P., Dierking, D. M., Johnson, T. A., Beauchaine, K. L., Garner, C. A., & Neely, S. T. (2005). A validation and potential clinical application of multivariate analyses of distortion-product otoacoustic emission data. *Ear and Hearing*, *26*(6), 593–607.

Gorga, M. P., Neely, S. T., Dorn, P. A., & Hoover, B. M. (2003). Further efforts to predict pure-tone thresholds from distortion product otoacoustic emission input/output functions. *The Journal of the Acoustical Society of America*, *113*(6), 3275–3284. https://doi.org/10.1121/1.1570433

Grothe, B., Pecka, M., & McAlpine, D. (2010). Mechanisms of sound localization in mammals. *Physiological Reviews*, *90*(3), 983–1012. https://doi.org/10.1152/physrev.00026.2009

Hackett, T. A. (2015). Anatomic organization of the auditory cortex. *Handbook of Clinical Neurology*, *129*, 27–53. https://doi.org/10.1016/b978-0-444-62630-1.00002-0

Harkins, S. W. (1981). Effects of age and interstimulus interval on the brainstem auditory evoked potential. *The International Journal of Neuroscience*, *15*(1–2), 107–118.

He, N., Dubno, J. R., & Mills, J. H. (1998). Frequency and intensity discrimination measured in a maximum-likelihood procedure from young and aged normal-hearing subjects. *The Journal of the Acoustical Society of America*, *103*(1), 553–565.

Hinojosa, R., & Nelson, E. G. (2011). Cochlear nucleus neuron analysis in individuals with presbycusis. *Laryngoscope*, *121*(12), 2641–2648. https://doi.org/10.1002/lary.22383

Hornsby, B. W., Johnson, E. E., & Picou, E. (2011). Effects of degree and configuration of hearing loss on the contribution of high- and low-frequency speech information to bilateral speech understanding. *Ear and Hearing*, *32*(5), 543–555. https://doi.org/10.1097/AUD.0b013e31820e5028

Hoth, S., Gudmundsdottir, K., & Plinkert, P. (2010). Age dependence of otoacoustic emissions: the loss of amplitude is primarily caused by age-related hearing loss and not by aging alone. *European Archives of Oto-Rhino-Laryngology*, *267*(5), 679–690. https://doi.org/10.1007/s00405-009-1106-5

Humes, L. E., Dubno, J. R., Gordon-Salant, S., Lister, J. J., Cacace, A. T., Cruickshanks, K. J., Gates, G. A., Wilson, R. H., & Wingfield, A. (2012). Central presbycusis: A review and evaluation of the evidence. *Journal of the American Academy of Audiology*, *23*(8), 635–666. https://doi.org/10.3766/jaaa.23.8.5

Humes, L. E., Kewley-Port, D., Fogerty, D., & Kinney, D. (2010). Measures of hearing threshold and temporal processing across the adult lifespan. *Hearing Research*, *264*(1–2), 30–40. https://doi.org/10.1016/j.heares.2009.09.010

Janssen, T. (2009). Otoakustische Emissionen. In E. Lehnhardt & R. Laszig (Eds.), *Praxis der Audiometrie* (9., vollst. überarb. Aufl. ed., pp. 113–136). Thieme.

Janssen, T., & Müller, J. (2008). Otoacoustic emissions as a diagnostic tool in a clinical context. In G. A. Manley, R. R. Fay, & A. N. Popper (Eds.), *Active processes and otoacoustic emissions in hearing*. Springer.

Jayakody, D. M. P., Friedland, P. L., Martins, R. N., & Sohrabi, H. R. (2018). Impact of aging on the auditory system and related cognitive functions: A narrative review. *Frontiers in Neuroscience*, *12*, 125. https://doi.org/10.3389/fnins.2018.00125

Johannesen, P. T., Perez-Gonzalez, P., Kalluri, S., Blanco, J. L., & Lopez-Poveda, E. A. (2016). The influence of cochlear mechanical dysfunction, temporal processing deficits, and age on the intelligibility of audible speech in noise for hearing-impaired listeners. *Trends in Hearing*, *20*, 233121651664105. https://doi.org/10.1177/2331216516641055

Keithley, E. M. (2020). Pathology and mechanisms of cochlear aging. *Journal of Neuroscience Research*, *98*(9), 1674–1684. https://doi.org/10.1002/jnr.24439

Keppler, H., Dhooge, I., Corthals, P., Maes, L., D'Haenens, W., Bockstael, A., Philips, B., Swinnen, F., & Vinck, B. (2010). The effects of aging on evoked otoacoustic emissions and efferent suppression of transient evoked otoacoustic emissions. *Clinical Neurophysiology*, *121*(3), 359–365. https://doi.org/10.1016/j.clinph.2009.11.003

Klinke, R., Pape, H.-C., & Silbernagl, S. (2005). *Physiologie* (5., komplett überarb. Aufl. ed.). Thieme.

Konrad-Martin, D., Dille, M. F., McMillan, G., Griest, S., McDermott, D., Fausti, S. A., & Austin, D. F. (2012). Age-related changes in the auditory brainstem response. *Journal of the American Academy of Audiology*, *23*(1), 18–35; quiz 74-15. https://doi.org/10.3766/jaaa.23.1.3

Kujawa, S. G., & Liberman, M. C. (2015). Synaptopathy in the noise-exposed and aging cochlea: Primary neural degeneration in acquired sensorineural hearing loss. *Hearing Research*, *330*(Pt B), 191–199. https://doi.org/10.1016/j.heares.2015.02.009

Kummer, P., Janssen, T., Hulin, P., & Arnold, W. (2000). Optimal L1–L2 primary tone level separation remains independent of test frequency in humans. *Hearing Research*, *146*(1–2), 47–56. https://doi.org/10.1016/S0378-5955(00)00097-6

Kuroda, T., Hasuo, E., & Grondin, S. (2013). Discrimination of brief gaps marked by two stimuli: effects of sound length, repetition, and rhythmic grouping. *Perception*, *42*(1), 82–94. https://doi.org/10.1068/p7186

Kuwada, S., Yin, T. C., & Wickesberg, R. E. (1979). Response of cat inferior colliculus neurons to binaural beat stimuli: Possible mechanisms for sound localization. *Science*, *206*(4418), 586–588.

Leaver, A. M., & Rauschecker, J. P. (2016). Functional topography of human auditory cortex. *The Journal of Neuroscience*, *36*(4), 1416–1428. https://doi.org/10.1523/jneurosci.0226-15.2016

Lee, K. Y. (2013). Pathophysiology of age-related hearing loss (peripheral and central). *Korean Journal of Audiology*, *17*(2), 45–49. https://doi.org/10.7874/kja.2013.17.2.45

Legatt, A. D. (2012). Brainstem auditory evoked potentials: Methodology, interpretation, and clinical application. In M. J. Aminoff (Ed.), *Aminoff's electrodiagnosis in clinical neurology* (6th ed., pp. 519–552). W.B. Saunders.

Lehnhardt, E., & Laszig, R. (2009). *Praxis der Audiometrie* (9., vollst. überarb. Aufl. ed.). Thieme.

Lenarz, T., & Boenninghaus, H.-G. (2012). *Hals-Nasen-Ohren-Heilkunde* (14., überarb. Aufl. ed.). Springer.

Liberman, M. C., & Kujawa, S. G. (2017). Cochlear synaptopathy in acquired sensorineural hearing loss: Manifestations and mechanisms. *Hearing Research*, *349*, 138–147. https://doi.org/10.1016/j.heares.2017.01.003

Ludwig, A. (2009). *Psychoakustische und elektrophysiologische Untersuchungen zu zentral-auditiven Verarbeitungsstörungen während der Kindesentwicklung* (Dissertation). Universität Leipzig, Leipziger Universitäts-Verlag, Leipzig. http://digitool.hbz-nrw.de:1801/webclient/DeliveryManager?pid=3140442 Universitätsbibliothek Leipzig database.

Lutz, J., Hemminger, F., Stahl, R., Dietrich, O., Hempel, M., Reiser, M., & Jager, L. (2007). Evidence of subcortical and cortical aging of the acoustic pathway: a diffusion tensor imaging (DTI) study. *Academic Radiology*, *14*(6), 692–700. https://doi.org/10.1016/j.acra.2007.02.014

Martini, A., Comacchio, F., & Magnavita, V. (1991). Auditory evoked responses (ABR, MLR, SVR) and brain mapping in the elderly. *Acta Oto-Laryngologica. Supplementum*, *476*, 97–104.

Mathers, C., Smith, A., & Concha, M. (2000). *Global burden of hearing loss in the year 2000*. http://www.who.int/healthinfo/statistics/bod_hearingloss.pdf

Middlebrooks, J. C. (2015). Sound localization. *Handbook of Clinical Neurology*, *129*, 99–116. https://doi.org/10.1016/b978-0-444-62630-1.00006-8

Mrowinski, D. (2009). Elektrische Reaktionsaudiometrie. In E. Lehnhardt & R. Laszig (Eds.), *Praxis der Audiometrie* (9., vollst. überarb. Aufl. ed., pp. XII, 268 S.). Thieme.

Mrowinski, D., & Scholz, G. (2011). *Audiometrie: eine Anleitung für die praktische Hörprüfung* (4., aktualisierte und erw. Aufl. ed.). Thieme.

Nadol, J., Jr. (2010). Disorders of aging. In S. N. Merchant & H. F. Schuknecht (Eds.), *Schuknecht's pathology of the ear*. People's Medical Publ. House.

Nakashima, T., Miller, J. M., & Nuttall, A. L. (1995). Autoregulation of cochlear blood flow in young and aged mice. *European Archives of Oto-Rhino-Laryngology*, *252*(5), 308–311.

Nelson, E. G., & Hinojosa, R. (2006). Presbycusis: A human temporal bone study of individuals with downward sloping audiometric patterns of hearing loss and review of the literature. *Laryngoscope*, *116*(Suppl. 112), 1–12. https://doi.org/10.1097/01.mlg.0000236089.44566.62

Neumann, K., & Rübsamen, R. (2005). Zentrale Hörstörungen bei hirngeschädigten Erwachsenen. In S. Jochims (Ed.), *Musiktherapie in der Neurorehabilitation internationale Konzepte, Forschung und Praxis*. Hippocampus-Verlag.

Oeken, J., Lenk, A., & Bootz, F. (2000). Influence of age and presbyacusis on DPOAE. *Acta Oto-Laryngologica*, *120*(3), 396–403.

Oku, T., & Hasegewa, M. (1997). The influence of aging on auditory brainstem response and electrocochleography in the elderly. *ORL: Journal for Otorhinolaryngology and Its Related Specialties*, *59*(3), 141–146.

Olusanya, B. O., Davis, A. C., & Hoffman, H. J. (2019). Hearing loss grades and the International classification of functioning, disability and health. *Bulletin of the World Health Organization*, *97*(10), 725–728. https://doi.org/10.2471/blt.19.230367

Ortmann, A. J., & Abdala, C. (2016). Changes in the compressive nonlinearity of the cochlea during early aging: Estimates from distortion OAE input/output functions. *Ear and Hearing*, *37*(5), 603–614. https://doi.org/10.1097/aud.0000000000000319

Ottaviani, F., Maurizi, M., D'Alatri, L., & Almadori, G. (1991). Auditory brainstem responses in the aged. *Acta Oto-Laryngologica. Supplementum*, *476*, 110–113.

Ouda, L., Profant, O., & Syka, J. (2015). Age-related changes in the central auditory system. *Cell and Tissue Research*, *361*(1), 337–358. https://doi.org/10.1007/s00441-014-2107-2

Ozmeral, E. J., Eddins, A. C., Frisina, D. R., Sr., & Eddins, D. A. (2016). Large cross-sectional study of presbycusis reveals rapid progressive decline in auditory temporal acuity. *Neurobiology of Aging*, *43*, 72–78. https://doi.org/10.1016/j.neurobiolaging.2015.12.024

Peñaranda, D., Pérez-Herrera, L. C., Hernández, D., Moreno-López, S., Perea, I., Jacome, M., Suetta-Lugo, N., García, J. M., & Peñaranda, A. (2021). Prevalence of extended high-frequency hearing loss among adolescents from two rural areas in Colombia. *International Journal of Audiology*, *60*(5), 365–373. https://doi.org/10.1080/14992027.2020.1828631

Pickles, J. O. (2015). Auditory pathways: anatomy and physiology. *Handbook of Clinical Neurology*, *129*, 3–25. https://doi.org/10.1016/b978-0-444-62630-1.00001-9

Profant, O., Balogova, Z., Dezortova, M., Wagnerova, D., Hajek, M., & Syka, J. (2013). Metabolic changes in the auditory cortex in presbycusis demonstrated by MR spectroscopy. *Experimental Gerontology*, *48*(8), 795–800. https://doi.org/10.1016/j.exger.2013.04.012

Profant, O., Jilek, M., Bures, Z., Vencovsky, V., Kucharova, D., Svobodova, V., Korynta, J., & Syka, J. (2019). Functional age-related changes within the human auditory system studied by audiometric examination. *Frontiers in Aging Neuroscience*, *11*, 26. https://doi.org/10.3389/fnagi.2019.00026

Profant, O., Skoch, A., Balogova, Z., Tintera, J., Hlinka, J., & Syka, J. (2014). Diffusion tensor imaging and MR morphometry of the central auditory pathway and auditory cortex in aging. *Neuroscience*, *260*, 87–97. https://doi.org/10.1016/j.neuroscience.2013.12.010

Profant, O., Tintera, J., Balogova, Z., Ibrahim, I., Jilek, M., & Syka, J. (2015). Functional changes in the human auditory cortex in ageing. *PLoS One*, *10*(3), e0116692. https://doi.org/10.1371/journal.pone.0116692

Prosser, S., & Rosignoli, M. (1992). Observations on the ABR I-V interval in a clinical sample of elderly patients. *British Journal of Audiology*, *26*(5), 271–274.

Pürner, D. L. (2019). *Änderungen der peripheren und zentralen Schallverarbeitungsleistungen mit dem Alter* (Thesis). Technical University of Munich, München.

Rosen, S., Bergman, M., Plester, D., El-Mofty, A., & Satti, M. H. (1962). Presbycusis study of a relatively noise-free population in The Sudan. *The Annals of Otology, Rhinology, and Laryngology*, *71*(3), 727–743. https://doi.org/10.1177/000348946207100313

Rosenhall, U., Bjorkman, G., Pedersen, K., & Kall, A. (1985). Brainstem auditory evoked potentials in different age groups. *Electroencephalography and Clinical Neurophysiology*, *62*(6), 426–430.

Rosenhall, U., Moller, C., & Hederstierna, C. (2013). Hearing of 75-year old persons over three decades: has hearing changed? *International Journal of Audiology*, *52*(11), 731–739. https://doi.org/10.3109/14992027.2013.808381

Rosner, T. R. (2011). *Zeitoptimierte Hörschwellenbestimmung mit otoakustischen Emissionen und auditorischen Potentialen* (Dissertation). Technische Universität München, Verlag Dr. Hut, München.

Roth, T. N. (2015). Aging of the auditory system. *Handbook of Clinical Neurology*, *129*, 357–373. https://doi.org/10.1016/b978-0-444-62630-1.00020-2

Salminen, N. H., Takanen, M., Santala, O., Lamminsalo, J., Altoe, A., & Pulkki, V. (2015). Integrated processing of spatial cues in human auditory cortex. *Hearing Research*, *327*, 143–152. https://doi.org/10.1016/j.heares.2015.06.006

Schreiner, C. E., & Malone, B. J. (2015). Representation of loudness in the auditory cortex. *Handbook of Clinical Neurology*, *129*, 73–84. https://doi.org/10.1016/b978-0-444-62630-1.00004-4

Schuknecht, H. F. (1955). Presbycusis. *Laryngoscope*, *65*(6), 402–419. https://doi.org/10.1288/00005537-195506000-00002

Schuknecht, H. F., & Gacek, M. R. (1993). Cochlear pathology in presbycusis. *The Annals of Otology, Rhinology, and Laryngology*, *102*(1 Pt 2), 1–16. https://doi.org/10.1177/00034894931020s101

Sergeyenko, Y., Lall, K., Liberman, M. C., & Kujawa, S. G. (2013). Age-related cochlear synaptopathy: An early-onset contributor to auditory functional decline. *The Journal of Neuroscience*, *33*(34), 13686–13694. https://doi.org/10.1523/jneurosci.1783-13.2013

Shi, X. (2011). Physiopathology of the cochlear microcirculation. *Hearing Research*, *282*(1–2), 10–24. https://doi.org/10.1016/j.heares.2011.08.006

Slade, K., Plack, C. J., & Nuttall, H. E. (2020). The effects of age-related hearing loss on the brain and cognitive function. *Trends in Neurosciences*, *43*(10), 810–821. https://doi.org/10.1016/j.tins.2020.07.005

Sun, Z., Cheng, Z., Gong, N., Xu, Z., Jin, C., Wu, H., & Tao, Y. (2021). Neural presbycusis at ultra-high frequency in aged common marmosets and rhesus monkeys. *Aging (Albany NY)*, *13*(9), 12587–12606. https://doi.org/10.18632/aging.202936

Suzuki, T., Ren, T., Nuttall, A. L., & Miller, J. M. (1998). Age-related changes in cochlear blood flow response to occlusion of anterior inferior cerebellar artery in mice. *The Annals of Otology, Rhinology, and Laryngology*, *107*(8), 648–653. https://doi.org/10.1177/000348949810700803

Tadros, S. F., Frisina, S. T., Mapes, F., Kim, S., Frisina, D. R., & Frisina, R. D. (2005). Loss of peripheral right-ear advantage in age-related hearing loss. *Audiology & Neuro-Otology*, *10*(1), 44–52. https://doi.org/10.1159/000082307

Tawfik, K. O., Klepper, K., Saliba, J., & Friedman, R. A. (2020). Advances in understanding of presbycusis. *Journal of Neuroscience Research*, *98*(9), 1685–1697. https://doi.org/10.1002/jnr.24426

Trepel, M. (2008). *Neuroanatomie: Struktur und Funktion* (4., neu bearb. Aufl. ed.). Elsevier, Urban & Fischer.

Uchida, Y., Ando, F., Shimokata, H., Sugiura, S., Ueda, H., & Nakashima, T. (2008). The effects of aging on distortion-product otoacoustic emissions in adults with normal hearing. *Ear and Hearing*, *29*(2), 176–184.

Ueberfuhr, M. A., Fehlberg, H., Goodman, S. S., & Withnell, R. H. (2016). A DPOAE assessment of outer hair cell integrity in ears with age-related hearing loss. *Hearing Research*, *332*, 137–150. https://doi.org/10.1016/j.heares.2015.11.006

Ventry, I. M., & Weinstein, B. E. (1982). The hearing handicap inventory for the elderly: A new tool. *Ear and Hearing*, *3*(3), 128–134.

Ventry, I. M., & Weinstein, B. E. (1983). Identification of elderly people with hearing problems. *ASHA*, *25*(7), 37–42.

Wagener, K., Brand, T., & Kollmeier, B. (1999a). Entwicklung und Evaluation eines Satztests für die deutsche Sprache Teil II: Optimierung des Oldenburger Satztests. *Zeitschrift für Audiologie*, *38*(2), 44–56.

Wagener, K., Brand, T., & Kollmeier, B. (1999b). Entwicklung und Evaluation eines Satztests für die deutsche Sprache Teil III: Evaluation des Oldenburger Satztests. *Zeitschrift für Audiologie*, *38*(3), 86–95.

Wagener, K., Kühnel, V., & Kollmeier, B. (1999). Entwicklung und Evaluation eines Satztests für die deutsche Sprache I: Design des Oldenburger Satztests. *Zeitschrift für Audiologie*, *38*(1), 4–15.

Wang, S. J., Furusho, M., D'Sa, C., Kuwada, S., Conti, L., Morest, D. K., & Bansal, R. (2009). Inactivation of fibroblast growth factor receptor signaling in myelinating glial cells results in significant loss of adult spiral ganglion neurons accompanied by age-related hearing impairment. *Journal of Neuroscience Research*, *87*(15), 3428–3437. https://doi.org/10.1002/jnr.22164

Weinstein, B. E. (1986). Validity of a screening protocol for identifying elderly people with hearing problems. *ASHA*, *28*(5), 41–45.

Weinstein, B. E., & Ventry, I. M. (1983). Audiometric correlates of the Hearing Handicap Inventory for the elderly. *The Journal of Speech and Hearing Disorders*, *48*(4), 379–384.

Weiß, C. (2013). *Basiswissen medizinische Statistik: [mit Epidemiologie]; mit … 20 Tabellen* (6., überarb. Aufl. ed.). Springer.

World Health Organization. (1991). *Report of the informal working group on prevention of deafness and hearing impairment programme planning*. World Health Organization. https://apps.who.int/iris/handle/10665/58839

Wu, P. Z., O'Malley, J. T., de Gruttola, V., & Liberman, M. C. (2020). Age-related hearing loss is dominated by damage to inner ear sensory cells, not the cellular battery that powers them. *The Journal of Neuroscience*, *40*(33), 6357–6366. https://doi.org/10.1523/jneurosci.0937-20.2020

Wu, P. Z., O'Malley, J. T., de Gruttola, V., & Liberman, M. C. (2021). Primary neural degeneration in noise-exposed human cochleas: Correlations with outer hair cell loss and word-discrimination scores. *The Journal of Neuroscience*, *41*(20), 4439–4447. https://doi.org/10.1523/JNEUROSCI.3238-20.2021

## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

**Supplementary S1**

Transparent Science Questionnaire for Authors

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