The Auditory System
and
Its Relation to Cognitive Function
in the Process of Aging

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List of Abbreviations

dB	decibel
GABA	Gamma-Aminobutyric Acid
GOESA	Göttinger Satztest
HbA1c	Glycated Hemoglobin
HL	Hearing Level
HsCRP	High-sensitivity C-reactive Protein
IL-6	Interleukin-6
M	Mean
MDP	Melody Discrimination Performance
MMSE	Mini-Mental-State Examination
MRI	Magnet Resonance Imaging
MWT-B	Mehrfachwahl-Wortschatz-Intelligenztest
PEBL	Psychology Experiment Building Language
PTA	Pure-tone Average
ROI	Region of Interest
SD	Standard Deviation
SRT	Speech Reception Threshold
SSI	Sensorimotor Simultaneity Index

VLMT	Verbal Learning and Memory Test
TMT	Trail-making Test
WHO	World Health Organization
WRCM	Word Recognition in Competing Message

Abstract

Age-related hearing loss is a disabling condition that has been associated with many other negative health outcomes. Age-related hearing loss prevalence is high and strongly increases with age. Given the aging of western populations, hearing loss poses an increasing public health burden. The Rhineland Study is a large prospective cohort study that investigates age-related and neurodegenerative diseases and is well suited to investigate age-related hearing loss.

The main aim of this thesis was to gain insight into the etiology of and potential treatment strategies for age-related hearing loss. Specifically, I wanted to (1) assess to what extent hearing sensitivity and different cognitive functions influence central auditory processing across the adult life span in the population of the Rhineland Study; (2) investigate the benefit of motor synchronization on auditory performance and whether previous musical training and cortical thickness of specific brain regions relate to different aspects of this auditory-motor synchronization process in a student pilot population of the Rhineland Study; and (3) assess the temporal relations of hearing sensitivity, central auditory processing, and cognition by using longitudinal data from the Beaver Dam Offspring Study.

In the cross-sectional analysis based on the Rhineland Study, I found that hearing sensitivity is most important for speech understanding in noise. Furthermore, crystallized intelligence and executive functions showed effects on speech understanding in noise as opposed to memory functions, which seemed less important for this ability. I concluded therefore that the ability to perceive speech signals seems to play a major role in speech understanding in noise. Higher-order cognitive functions may be beneficial at a later speech processing stage, with different involvement of different cognitive functions.

In the experiment conducted in a student population, I identified a beneficial effect of motor synchronization on melody discrimination ability. Previous experience in musical training and anatomical variability of relevant brain regions were associated with different aspects of this auditory-motor synchronization. These results suggest improved perception of complex auditory stimuli with auditory-motor synchronization. Moreover, prior

experience and structural brain differences influence the extent to which an individual can benefit from motor synchronization in a complex listening task.

In the longitudinal analyses of the Beaver Dam Offspring Study data, I found that baseline hearing sensitivity more strongly affected later higher-order central auditory processing than vice versa. The associations between hearing and cognition were bidirectional and weak. This suggests that loss of hearing ability and cognitive decline may share a common cause rather than impairment in one function preceding and triggering impairment in the other. Therefore, hearing improvement may have only a limited benefit for prevention or delay of cognitive decline.

In conclusion, the work in this thesis contributes to our understanding of the etiology of age-related hearing loss and its relation to cognitive decline. The findings in this thesis will be of benefit to future studies directed at deepening the knowledge on age-related hearing loss and the development of potential treatment strategies for age-related hearing loss.

1 Introduction

"Blindness separates people from things, deafness separates people from people."

This quote has been attributed to Helen Keller who was a blind and deaf American writer and social activist. In more detail she wrote in a letter in 1910: "The problems of deafness are deeper and more complex, if not more important, than those of blindness. Deafness is a much worse misfortune. For it means the loss of the most vital stimulus – the sound of the voice that brings language, sets thoughts astir and keeps us in the intellectual company of man." (Keller, 1933, p.68) This quote expresses the importance of hearing function for speech understanding as an essence of social interaction. Impaired speech understanding (e.g. as a result of age-related hearing loss) therefore has the potential to severely impact human lives.

Hearing loss is the most common sensory impairment, and age-related hearing loss, also called presbycusis, is among the top ten leading causes for years lived with disability.[2] In 2018, 466 million people (6.1% of the world population) lived with a disabling hearing loss, most of which was due to age-related hearing loss.[3] Age-related hearing loss is highly prevalent and strongly increases with age.[4–6] Due to aging populations, the number of people with hearing loss worldwide is expected to double by 2050.[3] Therefore, the burden of hearing loss will only further increase and become a major public health concern.

To date, no cure for hearing loss exists.[7] Hearing aids are beneficial to increase audibility but the benefit is limited with regards to impairments in speech understanding, particularly in noisy environments.[8,9] However, people with hearing loss feel most handicapped about their impairment of understanding speech in background noise.[10] Improvement of existing treatments and the development of new treatments for speech understanding in noise is urgently needed. In order to develop such therapeutic and also prevention strategies we need to improve our understanding of the underlying pathophysiology and the determinants of speech understanding in noise.

Age-related hearing loss is not only a disabling condition in itself but has also been associated with negative health outcomes including emotional loneliness,[11] social isolation,[12] mental health and depression,[12,13] impairments in daily life activities, and reduced quality of life.[13,14] In particular, the possible relation between hearing loss and cognitive decline[15,16] has gained increasing attention over the last years. However, the direction of this association and its underlying mechanisms are not well understood. It remains unclear whether hearing loss can contribute to cognitive decline, or developing cognitive changes lead to impaired speech perception, or whether they share a common cause. Investigating this relationship will improve our understanding of the etiology of both hearing loss and cognitive decline and will help to determine if, and to what extent, improved hearing could potentially prevent or delay cognitive decline.

1.1 Aim of This Thesis and Study Design

The aim of this thesis is to gain insights into the etiology and potential treatment strategies of age-related hearing loss. The studies presented in this thesis are based on two population-based cohort studies, the Rhineland Study and the Beaver Dam Offspring Study, as well as on a student pilot sample of the Rhineland Study.

1.2 Outline of This Thesis

In Chapter 2, I will present background information on age-related hearing loss. First, I will outline the symptoms of age-related hearing loss and underlying impairments in the peripheral and central hearing system, which contribute to the etiology of age-related hearing loss. Second, I will describe different approaches to measure hearing function. Next, I will give an overview on treatments and rehabilitation strategies for age-related hearing loss. Finally, I will discuss risk factors for age-related hearing loss and the current knowledge about the association of hearing impairment and cognitive decline.

Chapter 3 describes the Rhineland Study. After a short overview of the study aims and design, I will present those parts of the study protocol that I actively co-developed and implemented and that are relevant for the work described in this thesis, i.e. the hearing assessment and cognitive test battery.

Chapters 4, 5, and 6 present the three empirical studies of this thesis. Chapter 4 describes the cross-sectional examination of the determinants of central auditory processing in the Rhineland Study. Specifically, I investigated the relative effects of hearing sensitivity and different cognitive functions on speech in noise understanding. Chapter 5 presents an experimental investigation, which was conducted with a pilot sample of the Rhineland Study. I investigated the effects of auditory-motor synchronization as a potential facilitation strategy for auditory performance. Furthermore, I assessed how previous musical training and cortical thickness of specific brain regions relate to different aspects of this auditory-motor synchronization. Chapter 6 is based on a longitudinal analysis of data from the Beaver Dam Offspring Study, in which I investigated the temporal association of hearing and cognition in middle-aged adults.

The thesis concludes with Chapter 7, in which I discuss the main research findings in the context of current knowledge and clinical relevance, elaborate on relevant methodological aspects, and make suggestions for future research.

2 Age-related Hearing Loss

Age-related hearing loss is highly prevalent in older adults. According to the World Health Organization (WHO) the prevalence of disabling hearing loss in the population of people aged 65 years and older is almost twice as large in developing countries (estimates vary between 34–49%), compared to high-income countries (18%), with the exception of Middle East North Africa, which reportedly has a hearing loss prevalence of 26%.[3]

Prevalence rates vary strongly across studies (7.5–46%) due to different study designs, and age distributions.[4–6,17] Moreover, hearing loss definitions vary largely: The WHO defines disabling hearing loss as pure-tone audiometry average 0.5–4 kHz greater than 40 decibel (dB) in the better ear,[3] other studies set the cut-off at 25dB in the better ear[18] or worse ear.[4,5,19] In Germany, the prevalence of hearing loss in adults above the age of 18 has been reported as 15.7% in 2010–2012.[5] The overall five-year incidence of hearing impairment lies around 20% across different studies of elderly above the age of 48 years.[18,19] Prevalence rates[4–6,17] and incidence rates[18,19] strongly increase with age. Age-specific prevalence rates for hearing loss in elderly people are more than 30% for people in their 60s, more than 50% for people in their 70s, and more than 80% for the population above the age of 80.[4,5] The five-year incidence rate of hearing impairment is 23% for people in their 60s, 48% for people in their 70s, and 96% for people above the age of 80 years.[19] The age-specific prevalence of hearing loss declined over the last decades in western countries.[6,20]

Age-related hearing loss is characterized by a hearing sensitivity loss and reduced speech understanding, particularly in noisy environments. Further impairments include slowed central processing of acoustic information and impaired sound localization.[21] This thesis focuses primarily on impairments of hearing sensitivity loss and speech understanding.

Hearing sensitivity loss typically starts at higher frequencies and spreads to include mid and low frequencies with time.[22] In older adults, average hearing thresholds increase

approximately 1 dB per year,[23,24] while the decline of different frequencies varies slightly with age and sex.[22,25]

Performance on speech recognition in quiet[24] and in noise[26] decrease longitudinally. Decreased hearing sensitivity is associated with decreased speech understanding. However, age-related changes in speech recognition are often larger than expected by the degree of hearing sensitivity loss. This holds for both speech impairments in quiet[8,9,27–29] and in noise.[8,9,29–31]

2.1 Physiological Basis of Age-related Hearing Loss

The described symptoms of age-related hearing loss are a result of changes in the peripheral auditory system (the ear, including the cochlea and its afferent innervation) and the central auditory pathways (from the ear to auditory cortex). While the impairments in the peripheral and central auditory system will be presented separately, it is acknowledged that age-related hearing loss typically presents with co-occurring impairments in both cochlear and central processing systems.[32]

2.1.1 Impairments in the Peripheral Auditory System

Early work on the pathology of human age-related hearing loss came from the laboratory of Schuknecht, who investigated hearing loss in animals and human by combining premortem hearing tests with light microscopy of postmortem inner ears.[33,34] His lab described four distinct types of hearing loss: (1) sensory, typified by high frequency hearing loss attributed to cochlear hair cells loss, (2) metabolic, typified by flat hearing loss of lower frequencies attributed to atrophy in the lateral wall and the stria vascularis of the cochlea, (3) neural, typified by word discrimination impairments in the presence of stable hearing sensitivity thresholds attributed to ganglion cell loss, and (4) a hypothetical type of cochlear conductive, typified by stiffness of the basilar membrane.[34] Until now there has been little evidence for a biological basis of the hypothetical cochlear conductive subtype[35] and it is assumed that this type might be a severe form of the metabolic subtype.[36] In human studies, it is difficult to identify the reasons for and mechanisms of

changes in the human peripheral auditory system because of the inherent variability in genetics and differences in cumulated environmental exposures in aging adults. Animal research under controlled conditions supports all three mechanisms that have been suggested in human studies: (1) a loss of hair cells, (2) changes in the walls surrounding the cochlea, and (3) ganglion cell loss in the cochlear nerve.[36]

Hair cells are distributed along the basilar membrane of the cochlea. The cochlea is tonotopically organized – high frequencies are processed at the base and lower frequencies are processed with progression towards the apex. Therefore, the outer hair cells in different areas of the cochlea are specialized to amplify the signal of specific frequencies by increasing endocochlear potentials between intra- and extra-cochlear fluids. The deflection of inner hair cells leads to a transduction of the endocochlear potentials into a neuronal signal.[36] The investigation of hair cell loss in humans and animals showed a significant loss of outer hair cells and little loss of inner hair cells with aging.[34,37–39] While in humans outer hair cell loss has been found particularly in the basal cochlear region (coding high frequency thresholds),[34,37] animals raised in quiet environments often have outer hair cell loss starting at the apex (coding low frequencies)[39] or simultaneously in both the base and apex.[38] Hence, outer hair cell loss, occurring particularly in basal regions of the cochlea, has been attributed to environmental factors, to noise exposure[34,40] and to toxic agent exposure such as ototoxic drug use.[41] These factors are thought to mainly contribute to sensory hearing loss.[34]

Moreover, metabolic and vascular functions are important for hearing. Reduced cochlear blood flow has been shown to negatively effect cochlear function.[42–44] In the process of aging, vascular pathologies (blood vessel atrophy) occur.[45] The lateral wall of the cochlea changes its constitution[46] and degenerates, which is associated with a decrease in the endocochlear potentials.[47] Such reduced endocochlear potentials are associated with alleviated signal transduction and hearing loss.[48] Since these potential changes occur along the entire cochlea, originally, changes in the lateral wall and stria vascularis of the cochlea were attributed to the metabolic subtype with a flat audiogram and comparably strongly elevated hearing thresholds across lower frequencies.[34] However, decreasing endocochlear potentials could also contribute to high-frequency hearing loss. The signal amplification gain achieved by the outer hair cells is strongest for higher fre-

quencies and weakest for lower frequencies. Hence, decreasing endocochlear potentials should most strongly affect signal amplification of the highest frequencies.[48]

The third mechanism regarding age-related change is a decrease in auditory neuronal functioning. Reasons for this might be a degeneration of spiral ganglion cells at the receptors[34,49,50] and/or asynchronous firing activity along the nerve.[51] Experimentally-induced damage to hair cells and the stria vascularis have been associated with subsequent loss of ganglion cells.[52,53] However, the causes and effects of this are still poorly understood.[36]

While these distinct mechanisms for hearing loss have been identified, a remarkable proportion of hearing loss cases is diagnosed as mixed subtype with several pathologies.[34,54] Moreover, as the clinical distinction between sensory and neural lesions is often difficult and a sensory lesion may lead to secondary neural degeneration (and potentially vice versa), the combined term, sensorineural, has been established[55] and is widely used.

2.1.2 Impairments in the Central Auditory Processing System

In humans, aging is accompanied by a loss of gray and white matter in the whole brain and also in the temporal lobes,[56,57] where the auditory cortex is located. In addition, there is functional change with aging; e.g. elderly people with hearing impairment recruit wider cognitive brain regions during perceptional tasks.[58,59]

Lesions along the neural connections from the ear to the auditory cortex can affect hearing.[21] Different age-related changes have been found in animal studies along the whole pathway of auditory processing – affecting the brain stem, midbrain and thalamus nuclei, and auditory cortices.[60,61] Evidence comes from animal studies of different species, strains, and methods. A range of physiological, neurochemical, morphological, and functional changes occur with aging.[60,61] These changes include but are not restricted to: neuronal cell loss, changes in calcium-binding protein levels, neurotransmitter levels, and receptor density levels.[60,61] In particular, changes in the GABA (gamma-Aminobutyric acid)-ergic system, a major inhibitory neurotransmitter system in the cerebral cortex,[62] have been repeatedly reported.[60,61] To date, there is still limited under-

standing of the exact underlying molecular mechanisms in age-related changes in different auditory brain regions.[61]

2.2 Assessment of Age-related Hearing Loss

There are numerous methods to assess different aspect of hearing ability. Pure-tone audiometry and speech intelligibility tests are most widely used measures of hearing in both clinical and research settings. Other behavioral hearing tests assess specific aspects of hearing function like frequency discrimination, intensity discrimination, sound localization, and auditory temporal processing.[32] Electrophysiological and electroacoustic measures are used to objectively assess hearing ability. Self-report information on hearing ability from questionnaires or interviews can evaluate subjective hearing ability. Furthermore, recent research acknowledges the fact that people with the same behavioral performance might have different costs and efforts to achieve this level of performance. Listening effort can be evaluated by assessing deviating physiological responses or brain activation during perceptional tasks.[63]

2.2.1 Pure-tone Audiometry

Pure-tone audiometry is considered the gold standard of measuring hearing acuity.[64] This standardized assessment of the ability to detect quiet tones of varying frequency has been conducted for more than 80 years.[65] To measure hearing sensitivity through audiometry, calibrated sounds of varying levels are presented to the individual. The lowest level to which the individual repeatedly reacts is considered the threshold at that frequency. The stimuli can either be presented through air conduction (using earphones or a loudspeaker) or bone conduction (using a bone oscillator placed on the mastoid bone). While air conduction measures the function of the entire auditory system, bone conduction circumvents sound propagation through the auditory canal and middle ear ossicles. A difference between air and bone conduction thresholds indicates impairments in the middle or outer ear and therefore the presence of conductive hearing loss.[66]

The presented stimuli are pure tones that are tones with a sinusoidal acoustic pressure waveform. For clinical purposes, thresholds for hearing levels at different frequencies are oftentimes displayed on a decibel Hearing Level (dB HL) scale. This scale takes into account that normal human hearing ability varies over frequencies; it is best at frequencies 3000–4000 Hz and decreases to lower and higher frequencies. On this scale, 0 dB HL reflects normal hearing at all frequencies and elevated thresholds are plotted below this normal hearing zero-line.[66] Human conversational speech is restricted to a specific frequency band. Ordinary conversation ranges from 250 to 3000 Hz and the comprehension of certain consonants involves frequencies in the 2000 to 8000 Hz range. Thus, clinical audiometers often range from 250 to 8000 Hz.[67]

Pure-tone thresholds of different frequencies can be averaged (pure-tone average [PTA]) across different frequency bands. In research, definitions for hearing loss vary across studies with regards to the usage of averaged frequency bands, chosen cut-offs for definition of hearing loss, and usage of better or worse ear.[15] The WHO defines hearing loss based on the pure-tone thresholds of the frequencies 0.5, 1, 2, 4 kHz of the better ear and defines a (mild) hearing loss as an average deviation of more than 25 dB HL.[68]

2.2.2 Tests of Speech Understanding

Pure-tone hearing levels provide limited information on individuals' ability to hear spectrally complex sounds including speech.[66] They oftentimes do not adequately reflect the disability that individuals experience in daily life,[69] possibly because the degree of hearing sensitivity loss does not completely explain impairments in speech understanding, particularly in noise.[29,31,70]

Various behavioral tests allow the exploration of speech intelligibility.[32] Speech understanding can be tested in quiet or against different types of background noise.[71] Target stimuli vary between syllables, words or complete sentences[72] and the distractor noise can be several types of artificial noise, babble or meaningful message.[32,72] Presentations can be monaural or binaural and distractors can be presented in the same or opposite ear than the target message.[32] Outcomes are typically the percentage of correctly re-

called target messages[73] or a signal-to-noise ratio at which a particular target speech reception level was achieved.[74]

2.2.3 Task Impurity Problem

Different hearing measures have been used to detect abnormalities in particular processing steps of the hearing system. Some measures are considered to be more affected by altered cochlear function, whereas others are thought to be more reflective of changes in the central auditory processing system. Decreased hearing sensitivity caused by peripheral cochlear defects can be measured by pure tone audiometry.[67] More complex tasks (e.g. speech in competing message tasks) are more prone to detect central abnormalities and thus can be used as a proxy for central auditory processing ability.[75] Particularly, impairments in speech intelligibility in the presence of normal hearing acuity[66] and/or a difference between speech understanding thresholds in quiet and in noisy environments have been used to characterize central auditory processing disorder.[21] However, it needs to be acknowledged that pure-tone audiometry does not only reflect cochlear function; received pure tones need to be processed in auditory brain regions to be perceived. Additionally, with regards to speech understanding (in noise), the speech signals need to be received at the cochlear level before the information can be processed in auditory brain regions. This task impurity problem is further compounded by the necessity of cognitive functions for such test performances. The generation of a behavioral response needs cognitive function. For instance, working memory function is needed to retain the speech stimuli[76] before an answer is generated. To account for this complexity, a diagnosis of central auditory processing impairment is based on impairments in at least two or more central auditory processing functions, such as auditory discrimination, auditory temporal processing, sound localization, auditory performance in competing acoustic signals, and auditory performance with degraded acoustic signals.[77]

2.3 Treatment and Rehabilitation of Age-related Hearing Loss

Age-related hearing loss cannot be cured but several rehabilitation methods exist. Hearing aids, cochlear implants, and hearing-assistive technologies can improve audibility. Furthermore, instruction on device use, counseling, and speech perception training are considered beneficial.[7] Moreover, the field of regenerative medicine is evolving promising new technologies to regenerate hair cells and combat hearing loss.[78,79] To date, the primary focus in treating hearing loss is the improvement of sensory impairment through the use of hearing aids, and in severe cases, cochlear implants.[7] However, there is growing interest in the potential to facilitate people's auditory perceptual abilities through training methods.[80]

2.3.1 Hearing Aids

Hearing aids improve audibility and speech understanding through amplification of the auditory signal.[8,9,81,82] However, speech understanding does not exclusively rely on hearing sensitivity[8,24,27,29] but also on the integrity of the central processing system.[27] Hearing aids do not restore normal hearing.[8] They amplify signals and do not repair damage or reverse changes that happened to the peripheral and central auditory system. Therefore, hearing aids do not completely restore speech perception abilities, which is particularly exhibited in individuals' ability to process speech in noise.[8,9] Correspondingly, patients with impairments in speech in noise perception are often not satisfied with hearing aids[83] and 25% of hearing aid users report dissatisfaction with hearing aids in noisy situations.[84]

2.3.2 Speech Perception Trainings

As speech perception problems cannot be resolved using amplification, a number of speech perception trainings have evolved. The efficacy of such kind of trainings is still under debate. A systematic review[85] and a meta-analysis[86] investigated the effectiveness of auditory training programs in adults. Such intervention programs typically train speech recognition under adverse conditions, such as word or sentence recognition in noise.[87] The studies found small beneficial effects of auditory training on speech perception.[85,86] The authors, however, also acknowledged the lack of investigation of long-term

effects[86] and Henshaw and Ferguson gauged the effects as small and not robust, due to large heterogeneity among training methods and durations, outcome measures, and participants samples.[85] The results of more recent randomized controlled trials investigating the transfer effect of auditory training on untrained speech perception tasks are also conflicting. One study found an improvement after training,[88] one found only limited improvement,[89] and two found no effect of training.[90,91]

2.3.3 Musicianship and Auditory-motor Interaction

Life-long musicianship and early life musical training have been associated with improvements in motor and auditory processing.[92] Many previous studies compared brain morphology and auditory functions in musicians to non-musicians. Young musicians have morphological advances in frontal,[93,94] auditory,[93–95] and motor regions.[95] Additionally, various white matter tracts connecting frontal and temporal/auditory areas and between the hemispheres[96] as well as sensorimotor tracts[97] have been associated with musicianship. Furthermore, young musicians have shown better speech in noise perception and auditory processing as opposed to non-musicians.[98,99] While musical training has been well-studied in young adults, fewer studies examined the effects in older adults.[100] With respect to the elderly, musicians have been shown to have better cognitive function,[101] auditory processing performance,[102,103] and auditory discrimination ability.[104,105] Furthermore, age effects on speech in noise performance were less substantial in musicians.[105] However, conclusions from such cross-sectional studies on musicians cannot extract the pure effect of musical training, as residual confounding (e.g. of general cognitive abilities or personality) might exist.[106]

Experimental results of even relatively short-term musical training have been associated with changes in brain morphology and physiology subserving auditory processing.[92] Early life musical training leads to morphological changes in auditory and motor brain regions and corresponding improvements in auditory and motor tasks.[107] In young adults, two weeks of piano training showed improvements in auditory stimuli induced brain reactivity of auditory regions, as well as in auditory discrimination ability[108,109] and four weeks of music-cued motor training increased white matter tracts connecting temporal and frontal brain regions.[110]

The strong auditory-motor interactions that are specific to music are considered one of the driving forces for neuronal plasticity.[92,111] A recent randomized controlled trial in 21 elderly and hearing impaired people showed benefits of an 8-week auditory-motor perceptual training. Here, participants used auditory feedback to accurately move with their fingertip through a virtual soundscape. After training speech intelligibility in background noise was improved, however, the improvement was not stable without continuous training.[112]

Furthermore, several studies have begun to explore whether the synchronization of motor performance with auditory input can enhance auditory perception and obtained promising results. Motor-synchronization has been shown to improve rhythm and timing perception[113–115] as well as pitch discrimination.[116]

2.4 Risk Factors of Age-related Hearing Loss

A variety of factors including genetic susceptibility, environmental factors, health comorbidities, and lifestyle contribute to the etiology of hearing loss. These effects accumulate and have potentially complex interactions. While genetic factors may play a more important role in disease etiology in early-onset hearing loss, environmental factors are especially important for hearing loss later in life.[117] Many cross-sectional studies exist, but fewer studies prospectively evaluate risk factors for hearing loss. Therefore, it remains unclear whether many of these factors also prospectively contribute to incidence and/or progression of hearing impairment.[64]

2.4.1 Genetic Predispositions and Sex

Heritability indices of hearing loss vary largely across samples, measures, and definition of hearing ability between 25% and 75%.[118–121] To date, the genetic field of age-related hearing loss is still very small.[122] Age-related hearing loss is a multifactorial and polygenic disease,[123] which implies that the involvement of many loci of small effects is very likely.[122] Genetic association studies reveal inconsistent results.[123–126] This might be attributable to inadequate sample size, differences in environmental exposure, publication

bias, population stratification, and/or variation in phenotypic classification and measurements.[122] A recent whole-genome sequencing study identified two potential candidate genes (CUB and Sushi multiple domains 1 [*CSMD1*] and receptor-type tyrosine-protein phosphatase delta [*PTPRD*]) that were also identified in a previous genome wide association study and are likely to have a functional role in age-related hearing loss.[127]

There are significant sex differences in age-related hearing loss; men have been found to be at a higher risk of developing hearing loss than women. The exact risk ratios vary across study samples from a 2-fold to a 5.5 fold increased risk.[4,6,17] After adjustment for age, education, occupation, and noise exposure, Cruickshanks and colleagues reported a more than 3 times higher risk for men than for women.[4] Men have also been reported to have worse word recognition scores in quiet and in noise[26,29,128] with one exception.[129] Different explanations for this sex difference exist. Men might be more likely to being exposed to noise in occupational settings. However, since an increased risk remains after adjusting for those factors, also other factors might be relevant.[4] Men show higher rates of potential risk factors for hearing loss, such as smoking and cardiovascular factors which might contribute to their excessed risk.[130]

Furthermore, racial differences in the prevalence of age-related hearing loss have been described. African Americans have repeatedly shown to have a lower prevalence of hearing loss than Caucausians[6,17,131] and Hispanics.[6] The underlying mechanisms of these race differences in hearing loss are not well understood.[131] With regards to the advantage of African Americans, it has been suggested that they might be less susceptible to noise-induced hearing loss[132,133] and higher melanin levels in the inner ear have been hypothesized as an underlying protective factor.[134]

2.4.2 Environmental Factors

Socio-economic status has been identified as a risk factor for hearing impairment with the usage of various operationalizations of socio-economic status. Effects of area of residence,[129] occupation,[4] income,[4] and education[4,6,17] have been shown. People with a lower socio-economic status on average have a less healthy lifestyle,[135] which might be one reason for an effect of socio-economic status on hearing. Another reason may be

that they are more likely to be exposed to possible damaging effects (e.g. noisy occupations).[4]

As outlined above, hearing loss might also be attributable to the accumulation of noise and toxic agent exposure throughout life.[21,36] Pharmacological studies suggest irreversible ototoxic effects of some chemotherapeutic agents and aminoglycoside antibiotics, and potentially reversible effects of macrolides, antimalarials, loop diuretics, and high-dose salicylates.[41] This has been confirmed on a population level where ototoxic medication users showed an increased prevalence of hearing impairment.[129] Some chemicals and heavy metals have also been identified as ototoxic agents. Exposure to chemical organic solvents[136] and heavy metal concentration in blood[137,138] have shown negative effects on hearing function.

Effects of noise exposure on irreversible outer hair cell loss and co-occurring reduced hearing sensitivity have been shown.[34,40] Thus, an accumulation of lifetime noise exposure effects on hearing abilities seems plausible,[139] and the relationship of high occupational noise exposure and decreased hearing function has been reported repeatedly.[4,129,131,140] However, other studies failed to find an effect of noise exposure history on longitudinal hearing threshold change[25,141] and of accumulated lifetime noise exposure on hearing abilities.[142,143] Therefore, the effect of noise exposure on a population basis might also reflect other factors and occupational noise exposure might not play such an important role in hearing impairment in older adults.[141]

2.4.3 Medical Comorbidities and Lifestyle

Obstruction or disease of the outer or middle ear can prevent transmission of sound energy to the inner ear and lead to a conductive hearing loss. Cerumen impaction or fixation of one or more of the middle-ear bones, mainly fixation of the stapes due to otosclerosis can cause conductive hearing loss.[144] Those impairments affect the important amplifying effect of the middle ear and reduce thresholds across all frequencies.[66] While cerumen production seems to increase with age,[21] there is little evidence for substantial stiffening of the middle ear transmission system with age in older adults.[145] Furthermore, recurrent ear infections have been associated with hearing loss.[146,147]

Given the evidence for vascular mechanisms involved in the pathology of hearing loss,[34,45] an association of hearing loss with cardiovascular risk factors seems viable. Various studies with different assessments of cardiovascular risk factors have been conducted. Negative effects of hypertension,[129,148,149] cardiovascular disease,[129,148] and cerebrovascular disease[131] have been documented. Moreover, vessel thicknesses of macrovascular structures (carotid arteries) and microvascular structures (retinal vessels) were associated with hearing loss.[150]

Furthermore, higher body mass index[151] and cholesterol levels[152] contribute to cardiovascular disease. Accordingly, effects of higher body mass index on hearing loss were reported many times.[129,140,153] The association with cholesterol is less established. Some studies have found no association of total serum cholesterol with hearing,[148,150,154,155] others show a protective effect of high-density lipoprotein,[121] and one study shows a protective effect of total cholesterol.[156] A prospective study found small and clinically irrelevant negative effects of cholesterol on hearing levels that were not persistent longitudinally.[157] Results with regards to cholesterol regulating drug use were also contradictive.[150,154]

Diabetes mellitus has also been acknowledged as a risk factor for hearing loss[129,131,158,159] with a two-fold increased risk for hearing loss in diabetic patients (for a meta-analysis see[160]). Two possible underlying mechanisms that could explain this association are vascular and ototoxic effects. Both, cardiovascular disease[161] and vascular pathologies in the ear[162,163] have been linked to diabetes. On the other hand, nephrotoxic agents, besides their negative effect on the kidneys, may be ototoxic and cause hearing loss. Moreover, treatment for nephropathy may be ototoxic and confound this association.[158]

Smoking potentially affects the auditory system via ototoxic effects of inhaled substances and/or via attenuated vascular supply in the cochlea.[164,165] Correspondingly, smoking has been identified as a risk factor for hearing loss.[129,131,140,166,167] A two-fold increased risk was the summarized effect of cohort studies in a meta-analysis.[168]

Moderate alcohol consumption has been considered to be protective of coronary heart disease.[169] However, results with regards to hearing loss are conflicting. Some studies found this protective effect of moderate consumption on hearing function,[167,170,171] while others found protective effects of all doses,[129,140,159] and lastly one study did not find a prospective effect on incident hearing loss.[171]

2.5 Cognitive Decline and Age-related Hearing Loss

Cognitive decline has considerable consequences for quality of life and is a major concern in aging adults.[172] There were 47 million cases of dementia worldwide in 2015 and the number of those with dementia is expected to dramatically increase[173,174] to 102 million worldwide in 2040.[174]

The relationship between hearing loss and cognitive decline or dementia has been observed in a number of prospective studies (for meta-analyses see[15,16]). Most studies used hearing sensitivity measures[175–178] whereas central auditory processing has been less studied.[179–181] Large population-based studies that assess both aspects of age-related hearing loss – hearing sensitivity and central auditory processing – remain scarce.

While the association has been shown repeatedly, the mechanisms explaining the co-occurrence of hearing loss and cognitive decline are not well understood. Four competing theories about the association of sensory and cognitive decline exist. (1) The common-cause hypothesis[182] suggests a common underlying factor that drives age-related decline in both systems. (2) The cognitive-load-on perception hypothesis[182,183] claims that age-related cognitive decline drives or precedes sensory decline. In contrast, (3) the sensory deprivation hypothesis[182] and (4) the information degradation hypothesis[183] both assume that sensory decline precedes cognitive decline. Importantly, according to the (3) sensory deprivation hypothesis, only long and chronic deprivation of sensory input induces cognitive decline[182] potentially through altered brain structures,[184] while the (4) information degradation hypothesis suggests an immediate and potentially remediable effect.[183] Others have suggested that social isolation mediates the potential effect of

hearing loss on cognitive decline.[185] The theories are not mutually exclusive. Multiple processes are likely involved[186] and the decline in one pathway could consequentially affect the other.[187] To date, we do not know to what extent each of these mechanisms plays a role in declining hearing and cognition.

Given the high interest in a potential beneficial effect of hearing restoration on cognitive function, researchers started to investigate an effect of hearing aid use on cognitive function and found benefits in hearing aid users.[188,189] These studies investigated self-selected hearing aid use and verbal cognitive tests. Few randomized controlled trials have been conducted and present conflicting results. One trial found a benefit of hearing aid users in a visual task,[190] and one trial in a composite memory score with a high load on auditory stimulus material.[191] Two other studies found no effect using non-auditory material based tests only.[192,193]

3 Hearing and Cognitive Assessment in the Rhineland Study

3.1 The Rhineland Study

The Rhineland Study is a large community-based prospective cohort study that aims to invite up to 30,000 participants and started recruitment in 2016. This single-center study invites all inhabitants aged 30 years or over from two designated geographically defined areas in Bonn, Germany. The people living in those areas are predominantly German with Caucasian ethnicity. Participation is only possible upon invitation and regardless of health status. The only exclusion criterion is an inability to sufficiently understand and sign the informed consent. The study is scheduled to run for at least thirty years with re-examinations taking place every three to four years.[194]

The main objectives of the study are (1) to investigate modifiable and non-modifiable causes of neurodegenerative and other age-related diseases, (2) to find biomarker profiles to identify individuals at risk for such diseases, and (3) to investigate normal and pathological (brain) structure and function over the adult life course.[194]

The study utilizes a broad range of instruments, including physiological function assessments, imaging measures, biomarker material collection, and self-reported information. Measurements assess the sensory systems of hearing, vision, and smell, anthropometry and body composition, the cardiovascular system, physical activity and fitness, neurological function, gait, and cognitive function. Participants' health history, personality, diet, lifestyle, and medication use are being investigated in interviews and questionnaires. Blood, urine, stool, saliva, and hair are being collected. Eligible participants undergo a one hour 3 Tesla Magnet Resonance Imaging Scan.[194]

The study protocol has been approved by the ethics committee of the University of Bonn, Medical Faculty. We obtain written informed consent from all participants in accordance with the Declaration of Helsinki. No financial incentives are offered for study participation.[194]

3.2 Hearing Assessments

The hearing assessments in the Rhineland Study include measurements of hearing sensitivity, speech in noise understanding, tympanometry, and self-report on hearing health history and self-rated hearing ability. The combination of audiometry with a speech in noise test is an advantage of the Rhineland Study and emphasizes the importance of detecting hearing thresholds as well as the assessment of a more complex hearing function. Testing of speech in noise understanding is of particularly large value since it reflects individuals' perception of their handicap in everyday interactions.

We measure hearing sensitivity through air conduction hearing thresholds in dB HL from Automated Pure-tone Audiometry (HörTech GmbH, Oldenburg). We obtain thresholds for 0.5, 1, 2, 4, 6, 8, 10, 12.5, and 16 kHz in each ear in an automated procedure.[195–197] This automated procedure is very quick and requires little input from the examiner, which makes it less susceptible to examiner effects. The examination starts with the left ear at 1 kHz, and continues with 0.5 kHz and thereafter the remaining frequencies in increasing order. The frequencies of the right ear are then being assessed in the same order. For each frequency, the participant has up to seven attempts. The threshold at each frequency is generated by three consistent responses. In case of insufficiently consistent responses, the program assigns a missing (due to compliance) value. To speed up the protocol for hearing impaired individuals, the test takes into account the performance levels of earlier frequencies of the same individual and automatically adjusts the starting presentation volume of higher frequencies. Because high levels of noise can induce damage to the ear and due to time constraints, we decided to tune each frequency up to a maximum level of 60 dB. If a participant cannot perceive the tones at that level of 60 dB, a value of 65 dB is being assigned. Importantly, we included high and ultra-high frequency hearing thresholds as age-related hearing loss first and primarily affects hearing of higher frequencies.[22,198] In the process of data cleaning, conspicuous patterns in audiograms are being identified and screened. Audiograms with missing data due to inconsistent responses, gaps of >= 20 dB between neighbor frequencies, and/or unexpectedly high thresholds at older ages (age >= 65 years and threshold <= 20 dB in frequencies 8 kHz, 10 kHz, 12.5 kHz, and 16 kHz) are automatically detected and then manually screened. Single thresholds or whole audiograms can be flagged or excluded,

in case of expected invalidity due to technical or other errors (also taking the comment by the study technician on the examination into account). To estimate the average hearing sensitivity of speech frequencies, we calculate a pure-tone average of hearing thresholds at 0.5, 1, 2, and 4 kHz for the better-hearing ear according to WHO standards.[68] In order to increase completeness of the data, we applied some strategies for the use of missing data: In case of missing data for one ear, the average of the other ear is taken into account for this score. If one or more values of the better ear had an assigned threshold of 65 dB, an additional variable is created to identify those participants for which this value could potentially be an underestimation of their severity of hearing loss. Sensitivity analyses can be conducted with excluding participants with data on one ear only and those with potentially underestimated hearing loss.

Göttinger Satztest (GOESA, HörTech GmbH, Oldenburg) is a semi-automated speech in noise test consisting of short German sentences presented in variable sound level against a constant background of speech band noise (of 65 dB and in case of inability to hear it at 65 dB of 75 dB). Participants repeat 20 sentences as accurately as possible. Speech sound levels on each trial are adapted online in an alternating staircase procedure from which the 50% speech reception threshold (SRT) in decibels is computed as primary outcome.[74] This adaptive procedure can cover a wide range of hearing function with little bottom or ceiling effects. Participants with severe hearing loss who are unable to perceive the noise at 75 dB are not eligible to complete this test. The test uses sentences as speech material, which mirrors a realistic communication environment (as opposed to tests using single words or syllables).

Both hearing performance assessments are performed in a sound-treated booth (DIN ISO 8253). The tests are conducted with air conduction headphones (Sennheiser HDA 200 and 300) using a licensed automated hearing testing protocol (HörTech GmbH, Oldenburg) with a Windows computer and external sound card (Auritec Earbox EAR 3.0) calibrated according to German norms for audiometry testing (DIN ISO 8253) once every year.

We also conduct tympanometry to screen participants for impaired middle ear transmission.[199] In this test, the study technician places a probe into the ear canal of the partici-

pant. In order to achieve an air-tight seal in the participant's ear canal, the probe is fitted with an individually sized ear tip. During the measurement, the device measures the responses to a probe sound while generating different pressure levels within the ear. This way, the integrity of the middle ear transmission system can be assessed.[199] Due to time constraints, we conduct three attempts per ear. In case of inability to generate a tympanogram within three attempts, a special missing value is assigned. On average, 6% of all conducted examinations are missing due to this procedure. When the tympanogram was successfully generated, the study technician evaluates and grades it as either normal or abnormal. Impairments within the middle ear transmission system might lead to a misinterpretation of the air-conduction hearing measures. Therefore, individuals with impaired tympanometric functions can be excluded in sensitivity analyses.

We collect self-reported information on different aspects of hearing health history, including history of noise exposure, blast injury, and sudden hearing loss, hearing aid and cochlear implant use, and self-rated hearing ability and tinnitus (Supplementary Material 1, Table S3.1).

From the hearing assessment battery, we report back the results of the pure-tone audiometry. Participants receive an audiogram of their hearing thresholds for the frequencies 0.5, 1, 2, and 4 kHz, which displays the performance in both ears separately. Moreover, we report back their grade of hearing loss according to WHO standards, which can be normal hearing (PTA <= 25 dB), mild hearing loss (PTA from 26 to 40 dB), and moderate hearing loss (PTA from 41 to 60 dB).[200]

3.3 Cognitive Assessments

The neuropsychological battery of the Rhineland Study covers a broad range of cognitive domains, including verbal episodic memory, working memory, executive functioning, processing speed, and crystallized intelligence and includes the following tests: Verbal Learning and Memory Test, Digit Span Task, Corsi Block-tapping Test, Trail-making Test, Word Fluency Task, Mehrfachwahl-Wortschatz-Intelligenztest, Pro-saccade Task, and Anti-saccade Task (Figure 1).

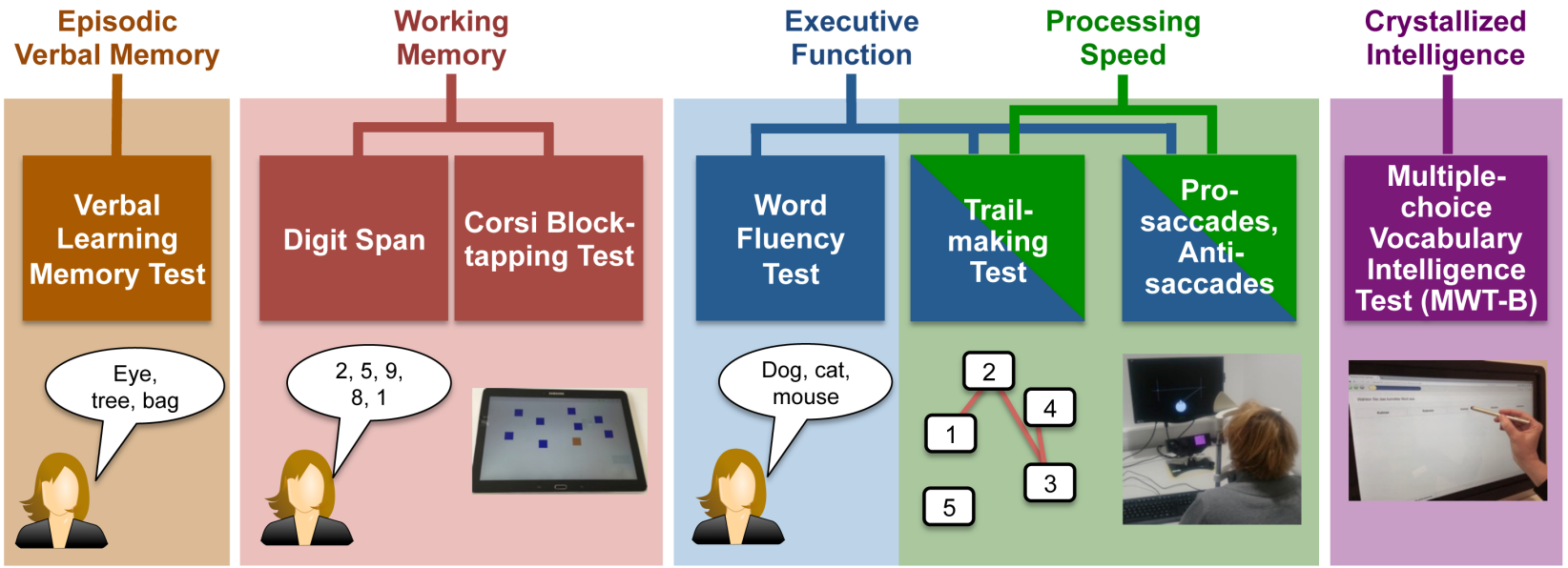

Figure 1. Cognitive Test Battery of the Rhineland Study.

All examinations are conducted by trained and certified study technicians according to standardized protocols. Different considerations went into the decision on the single tasks that compose this neuropsychological battery. One aim was to minimize the manual post-processing load. Therefore, touchscreen-based tests were preferred as opposed to paper-pencil test versions. Another advantage of the touchscreen-based tests is that they immediately acquire comprehensive data on test duration, performance, and types of error. However, the drawbacks of these tests are that some elderly people are not very familiar with the usage of touchscreens. To counteract these experience effects, participants are introduced into the usage of the screens and conduct training trials under the supervision of the study technician. Other tests are administered by the study technician and the results are immediately entered into a database. These tests are standardized and fairly easy to conduct by the examiner and do not require a neuropsychology background. A further challenge was to choose tests that are sensitive to change and performance across a wide age range from 30 years of age onwards. Tests should, as much as possible, have no bottom or ceiling effects. Tests with different sensory stimulus material and behavioral responses were chosen. This has the advantage to acquire cognitive data through different sensory systems, which limits the effect of sensory impairments on cognitive test performance. Effects of impairments in the different motor systems can also be limited this way. Cognitive domains (with the exception of crystallized intelligence) were represented by several tests. Lastly, another important aspect is the maintenance of participants' motivation and reduction of their concerns about their own performance. Tests that assess reaction time and tests without a predefined answer scale are particularly suitable for this. In those tests, participants do not know what the maximum performance level is and potentially perceive less feelings of failure.

A 15 words Verbal Learning and Memory Test (VLMT) analogous to the Rey Auditory Verbal Learning test[201,202] is administered by the study technician and used to measure short- and long-term memory. The test consists of five trials of learning and recall, an interference trial, and another immediate recall as well as a delayed recall after 20–30 minutes. Outcome measures are the number of correctly recalled items and the number of falsely named words in the respective trials. A learning curve over the course of the

trials, interference effects of the new list, and delayed long-term memory recall can be generated from the test. This study is conducted in a restricted local area and neighbors or relatives might verbally exchange about their experience during study participation. In order to avoid that participants know and practice the memory test word list before the testing, we developed ten parallel word lists during the pilot phase of the study. These lists have comparable difficulty levels and have been shown to appropriately cover a wide range of age-related performance levels. We randomly assigned one list to each participant.

The study technician administers the Digit Span forward and backward Task to assess verbal working memory. The participant is asked to recall sequences of digits in forward (sequence length 3–9) and backward order (sequence length 2–9) of increasing length. Two attempts are given per sequence length. The length of the last successfully completed sequence in the forward and backward version of the test, respectively, is a measure of the participant's forward and backward working memory span.

The Corsi Block-tapping Test measures visuo-spatial working memory. An adapted version from the Psychology Experiment Building Language (PEBL)[203] is conducted on a tablet PC (Samsung Galaxy note 10.1 2014 edition). Analogous to the verbal working memory test, the participant needs to recall visuo-spatial sequences of blocks changing color by tapping at the blocks in the correct order. After a supervised training session, the participant performs the test independently. Two attempts are given per sequence length. Forward and backward visuo-spatial working memory spans are measured by the length of the last successfully completed sequences in forward and backward versions, respectively. In the original PEBL version, feedback about the correctness of each trial is given.[203] We however, do not give feedback but the test is aborted after two incorrect trials. As opposed to the original manufactured version,[204] in addition to span length also reaction times and errors are recorded and can be used for future analyses.

An adapted version from the Trail-making Test (TMT) from the PEBL test battery[203] on a touchscreen (Touchscreen Dell Display S2240Tb) is used to assess processing speed and executive functioning. In version A, numbers are randomly scattered on the screen and the task is to connect the 24 digits via tap (1-2-3 etc.). In version B, digits from one

to twelve and letters from A to L are scattered on the screen and the task is to tap on and connect numbers and letters in ascending order in an alternating fashion (1-A-2-B etc.). After each correct tap, the items are being connected by lines by the software as a digital analogy to the original paper-pencil test.[205] After a supervised training session, the participant carries out the test independently. The time to completion in both versions is the main outcome. Inability to complete the test in allotted five minutes results in a score of 301 seconds. In order to closely relate to the original and most widely used paper-pencil version,[205] we decided to reduce the number of items in both versions. We used 24 digits in TMT A (instead of 26 in the PEBL version[203]) and 12 digits and 12 letters in TMT B (instead of 26 items in the PEBL version[203]). We also record various parameters of reaction time and error type that might be informative in future studies.

A Word Fluency Task is administered by the study technician and used to assess semantic memory and executive functioning. Participants have to name as many animals as possible within one minute. Performance is recorded during the session via audio recording and the outcome score (number of unique items) is graded by two independent graders. Apart from the count of correctly named items, word category (cluster) size and number of switches between word clusters are meaningful outcome variables.[206] More complex analyses on semantic or phonemic closeness and interrelations between words and clusters could be further investigated.

Crystallized intelligence is measured using the Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B), which is a German multiple-choice vocabulary and crystallized intelligence test.[207] In each of 37 trials, participants have to recognize one existing German word among four fictional words. After a supervised training session, the participant performs the test independently. The sum of correctly recognized words serves as a measure of crystallized intelligence.

As part of the neuropsychological assessment, an eye-tracking examination is conducted. The examination includes a Pro-saccade, Anti-saccade, Fixation, and Smooth Pursuit Task. The Pro-saccade and Anti-saccade Tasks are used as cognitive measures of attention, processing speed, and executive functioning. The examination is conducted in a darkened room with minimal ambient light. Participants sit in front of a height-

adjustable table with a 17-inch monitor and rest their chins on a chinrest. The distance between eyes and monitor is 70 cm. Oculomotor data are collected using the EyeLink 1000 and EyeLink 1000 Plus eye-tracker (SR Research Ltd., Mississauga, Ontario, Canada) with a sampling rate of 1,000 Hz at a spatial resolution of < 0.01° root mean square and an average accuracy of down to 0.15°. The eye movement task battery was developed in collaboration with the Cognitive Psychology Unit (Department of Psychology) of the University of Bonn and programmed using the SR Research Experiment Builder software (SR Research Ltd.). The stimulus used in all tasks is a white circle 1° in diameter presented on a black background. The Pro-saccade Task is a standard, horizontal "step" task. In each trial, the stimulus appears first in the central position (x = 0°, y = 0°) for a random duration of 1,000–2,000 ms (on average 1,500 ms). Then the stimulus steps to a peripheral position (x = ±15°, y = 0°) where it remains for 1,000 ms before returning to the center for the next trial. There are 30 trials with an equal number of right and left stimulus steps randomly ordered for each participant. Participants are instructed verbally and via text on the monitor to follow the stimulus as closely as possible. The Anti-saccade Task uses the same stimulus procedure as the Pro-saccade Task. The only difference lies in the instruction: In the Anti-saccade Task, participants are instructed to look at the stimulus when it is in the central position but to immediately look to the opposite (mirror image) position of the stimulus when it steps to the periphery. Various outcome parameters, including the latency, mean velocity, and error rates exist and are typically averaged over all valid trials. Advantages of the eye-tracking tasks are that they require little instruction, are hands- and language-free, and culture-fair.[208]

Since our cognitive battery covers many different cognitive functions, we also create cognitive domain scores and a global cognitive test score that reflects participants' general cognitive ability (Figure 1). We log10-transform the scores of tests with a skewed distribution (Trail-making Test A, Pro-saccade Task) and then generate z-standardized values for all tests. We reverse values from Trail-making Test and Pro- and Anti-saccade Task, so that higher values represent better performance for all cognitive tests. The single outcome scores from the different tests then contribute into domain scores for episodic verbal memory (VLMT immediate recall across trials 1 to 5 and delayed recall), working memory (Corsi Block-tapping Test and Digit Span Task forward and backward

span), executive functioning (Word Fluency Task, Trail-making Test B, and eye-tracker Anti-saccade Task error rate), processing speed (Trail-making Test A and eye-tracker Pro-saccade Task mean reaction time latency), crystallized intelligence (MWT-B). We calculate the domain scores as the averages of all z-standardized individual test scores per domain. For the calculation of a composite domain score for a participant, we require valid scores on at least 50% of the composing individual test scores to be present. Crystallized intelligence is represented by the z-standardized MWT-B test score only. Finally, we calculate a global cognitive performance as the z-score average of all domain scores except for crystallized intelligence. This global cognitive performance score is only calculated when all domain scores are present.

In the process of data cleaning and post-processing, non-native German speakers (defined by self-report), possible demented participants (defined by self-report and/or use of antidementia drugs), and individuals with severe cognitive impairment (defined by self-report) are being excluded from the generation of domain scores. These individuals are excluded from the generation of z-standardized scores, since they reflect a heterogeneous group of individuals, which might affect the standardization procedure. Moreover, regular quality checks on the distribution of all the acquired data are being conducted. We identify conspicuous data points through comparisons within age decades and/or combination of different measures. Extreme test scores (>2.2 interquartile ranges from median in each 10-year age group) are manually screened for each test outcome. We investigate potential invalidity due to technical or other errors (also taking the comment by the study technician on the examination into account). Finally, single test scores can be either excluded or marked within the usage of an additional variable, which then allows to exclude them in later sensitivity analyses.

4 Determinants of Central Auditory Processing – How Hearing Sensitivity and Cognitive Functions Affect Understanding of Speech in Noise

4.1 Abstract

Impaired speech understanding in noise is a symptom of age-related hearing loss, which is a common disabling condition and a health concern in the aging populations. Speech understanding in noise is considered to reflect impairments in higher-order central auditory processing and is thus often used as a marker of central auditory processing. The relative impact of hearing sensitivity loss and different cognitive functions on central auditory processing is not yet understood.

We aimed to assess to what extent hearing sensitivity and different cognitive functions influence central auditory processing across the life span.

This study is based on the first 1721 participants of the Rhineland Study, which is a community-based cohort study of persons aged 30 years and over. We measured speech understanding in noise, hearing sensitivity, and the following cognitive domains: crystallized intelligence, executive functioning, working memory, and long-term memory. We examined the association between hearing sensitivity and cognitive functions with central auditory processing with a multivariable linear regression model. We found that better hearing sensitivity, crystallized intelligence, and executive functioning but not memory were associated with better central auditory processing performance. Those results contribute to the understanding of age-related hearing loss.

4.2 Introduction and Aim

Few cohort studies investigated central auditory processing, whereas hearing sensitivity has been investigated more often.[16,187] Age-related changes in central auditory processing are not well understood. The degree to which decline in central auditory processing is independent of simultaneous age-related hearing sensitivity loss is still uncertain. Furthermore, the relation of central auditory processing to higher-order cognitive functions and the underlying mechanisms are still unclear.[32]

A recent meta-analysis of 1020 participants shows an association of central auditory processing and cognition across different cognitive functions. Nevertheless, the summarized studies are based on heterogeneous samples with different age ranges, levels of hearing sensitivity loss, and hearing aid user inclusion criteria.[72] A positive association of central auditory processing and different cognitive functions was also reported in cross-sectional UK Biobank data.[209] Previous studies did not control for hearing thresholds and/or did not assess different cognitive domains in one model. One cognitive measure does not only reflect the specific cognitive function that the test measures but also the general cognitive ability of the person. It is thus important to assess the relative effect of different cognitive functions to find out about underlying mechanisms.

We analyzed hearing sensitivity, central auditory processing, and four different cognitive functions in a population-based study including participants aged 30 years onwards. We aimed to assess to what extent hearing sensitivity and different cognitive functions influence central auditory processing ability across the adult life span.

4.3 Methods

4.3.1 Study Population

Our study population consisted of the first 2000 participants of the Rhineland Study who participated before 06/08/2018. The Rhineland Study is a community-based prospective cohort study that started recruitment in 2016. This single-center study invites all inhabit-

ants aged 30 years or over in designated geographically defined areas in Bonn, Germany. The people living in those areas are predominantly German with Caucasian ethnicity. Participation is only possible upon invitation and regardless of health status. Besides the age at study baseline, the inability to sufficiently understand the informed consent is the only exclusion criterion. Participants will be followed for thirty years with re-examinations taking place every three to four years. Approval to undertake the study was obtained from the ethics committee of the University of Bonn, Medical Faculty. We obtained written informed consent from all participants in accordance with the Declaration of Helsinki.

Participants were eligible for inclusion in the analyses, if they had a central auditory processing test score. We excluded participants who: were cochlear implant users, had possible dementia, had a history of traumatic brain injury, and/or were non-native speakers of German. Furthermore, participants who could not hear one or more of the four frequencies in the better ear at the maximum level of 60 dB HL, which resulted in imprecise hearing levels, were excluded.

4.3.2 Hearing Assessments

Audiometric assessments were performed by trained and certified examiners in a sound-treated booth (DIN ISO 8253). All hearing tests were conducted with air conduction headphones (Sennheiser HDA 200 and 300) using a licensed automated hearing testing protocol (HörTech GmbH, Oldenburg) with a Windows computer and external sound card (Auritec Earbox EAR 3.0) calibrated according to German norms for audiometry testing (DIN ISO 8253) once every year.

Central Auditory Processing

We measured central auditory processing using the Göttinger Satztest (HörTech GmbH, Oldenburg), which is a semi-automated speech in noise test consisting of short German sentences presented in variable sound levels against a constant background of speech band noise (of 65 dB). Participants repeated 20 sentences as accurately as possible. Speech sound levels on each trial were adapted online in an alternating staircase procedure. The 50% speech reception threshold in dB served as primary outcome[74] and

was our measure of central auditory processing ability. Higher values reflect worse performance.

Hearing Sensitivity

We obtained air conduction hearing thresholds in dB from Automated Pure-tone Audiometry (HörTech GmbH, Oldenburg) in each ear for 0.5, 1, 2, 4, 6, 8, 10, 12.5, and 16 kHz.[195,197] Maximum presentation volume was 60 dB HL for each frequency. We calculated the pure-tone average of hearing thresholds at 0.5 to 4 kHz for the better-hearing ear according to WHO standards[68] and used it as a measure of hearing sensitivity. Higher values reflect worse performance.

Besides audiometric assessments, we asked participants about their first language, hearing aid and cochlear implant use, and conducted tympanometry in order to assess participants' middle ear functioning.

4.3.3 Cognitive Assessments

A test battery of neuropsychological tests was administered in a quiet room by a trained and certified study technician to assess different cognitive domains.

Crystallized Intelligence

Crystallized intelligence was measured using the Mehrfachwahl-Wortschatz-Intelligenztest, which is a German multiple-choice vocabulary and crystallized intelligence test.[207] In each of 37 trials, participants have to recognize one existing German word among four fictional words. The sum of correctly recognized words serves as a measure of crystallized intelligence.

Executive Functioning

In order to assess executive functioning we used a digital version of the Trail-making Test adapted from the Psychology Experiment Building Language test battery[203] on a touch-screen (Touchscreen Dell Display S2240Tb). In TMT B, digits from one to twelve and letters from A to L were randomly scattered on the screen. The task was to tap on

and connect twelve numbers and letters in ascending order in an alternating fashion (1-A-2-B etc.) which were then connected by lines by the software as digital analogy to the original paper-pencil test.[205]

Working Memory

Working memory function was measured using the Digit Span Task. Here, participants were asked to forward recall sequences of digits of increasing length (sequence length 3–9). Two attempts were given per sequence length. The length of the last successfully completed sequence was a measure of the working memory span.

Long-term Memory

We assessed long-term memory with a German 15 words Verbal Learning and Memory Test analogous to the Rey Auditory Verbal Learning test.[201,202] The test consisted of five trials of learning and recall, an interference trial, and another immediate recall as well as a delayed recall after 20–30 minutes. We used one out of a set of ten parallel word lists per participant. The delayed recall was used as a measure of long-term memory.

4.3.4 Other Variables

As potential confounders we considered age, sex, income, education, hypertension (defined as systolic blood pressure >139 mmHg and/or diastolic blood pressure >89 mmHg and/or use of antihypertensive drugs), history of cardiovascular disease (defined as a report of coronary artery disease, stroke, peripheral arterial disease, heart insufficiency, myocardial infarction, peripheral, aorta, or carotid operation, and/or heart valve disorders), diabetes (defined as fasting glycated hemoglobin (HbA1c) > 6.4% and/or fasting glucose ≥ 126 mg/dL and/or use of antidiabetic drugs), possible dementia (defined as self-reported previous diagnosis and/or antidementia drug use), body mass index, ratio of non-high-density lipoprotein cholesterol and total cholesterol level, lipid-lowering medication intake, C-reactive protein level, depression (defined as antidepressant use), ototoxic medication intake (defined as intake of aminoglycosides, macrolides, quinine and its derivates, and loop diuretics), self-reported smoking history, tinnitus, and occupational noise exposure.

4.3.5 Statistical Analyses

We examined the associations between hearing sensitivity and cognitive functions with central auditory processing with multivariable linear regression models. We used speech in noise performance as outcome and pure-tone average and the different z-standardized cognitive scores as determinant variables. We log-transformed and inverted TMT B so that higher values in all cognitive measures represent better test performance. The coefficients of the regression model indicate speech reception threshold difference in dB. We adjusted for age (mean centered), age^2 (mean centered), sex, income, education, hypertension, history of cardiovascular disease, diabetes, body mass index, ratio of non-high-density lipoprotein cholesterol and total cholesterol level, lipid-lowering medication intake, C-reactive protein level, depression, ototoxic medication intake, smoking, tinnitus, and occupational noise exposure. Missing values for determinant variables varied from 1% (pure-tone average), 0.6–2.4% (cognitive scores) to 9.82% (smoking) and were imputed using multiple imputation. Twenty complete imputed datasets were created and regression analyses were performed on each dataset individually. Coefficients were pooled using Rubin's rules.[210] Statistical procedures were performed with statistical software RStudio Version 1.0.44[211] with packages dplyr,[212] mice,[213] miceadds,[214] and lattice.[215]

Sensitivity Analyses

To evaluate if relationships in hearing aid users as well as in participants with impaired middle ear function were the same as in the whole cohort, the model was repeated excluding hearing aid users and participants with abnormal tympanograms. We also performed the multivariable regression model in a complete cases dataset.

4.4 Results

We had to exclude cochlear implant users (n = 5), participants with possible dementia or a history of traumatic brain injury (n = 5), and non-native speakers of German (n = 141). Furthermore, there were 80 participants excluded who could not hear one or more of the four frequencies in the better ear at the maximum level of 60 dB HL, which resulted in imprecise hearing levels. Moreover, 48 participants had missing data in the speech in noise test. We included 1721 participants (57.2% women) with a mean (*M*) age of 54.5 (±13.5 standard deviation [*SD*]) years (Table 4.1) in our analyses.

Table 4.1. Characteristics of the Analytic Sample (n = 1721) of the Rhineland Study

Characteristic	
Age, yrs, *M (SD)*	54.5 (13.5)
Women, *n (%)*	985 (57.2)
Education, *n (%)*	
Below Bachelor's degree or equivalent	591 (34.7)
Bachelor's degree or equivalent or higher	1112 (65.3)
Hearing	
Ototoxic medication users, *n (%)*	26 (1.5)
Tinnitus, *n (%)*	155 (9.0)
Occupational noise exposed, *n (%)*	307 (19.1)
GOESA SRT, dB, *M (SD)*	-6.2 (1.3)
PTA, dB HL, *M (SD)*	13.8 (9.3)
Cognition	
MWT-B, n correct, *M (SD)*	30.5 (3.4)
TMT B, s, *M (SD)*	51.7 (34.4)
DS, n correct, *M (SD)*	6.4 (1.2)
VLMT, n correct, *M (SD)*	10.6 (3.1)
Comorbidities	
History of cardiovascular disease, *n (%)*	186 (10.8)
Hypertension, *n (%)*	649 (38.4)
Current smokers, *n (%)*	194 (12.5)
Diabetes, *n (%)*	64 (3.8)
Depression, *n (%)*	116 (6.8)

Note: *M*, mean; *SD*, standard deviation; GOESA, Göttinger Satztest; SRT, Speech Reception Threshold; PTA, pure-tone average 0.5–4 kilo Hertz; dB HL, decibel hearing level; MWT-B, Mehrfachwahl-Wortschatz-Intelligenztest; TMT B, Trail-making Test B; DS, Digit Span Task; VLMT, Verbal Learning and Memory Test

Increasing pure-tone average was associated with worse speech in noise performance (0.05 dB difference per 1 dB HL; 95% CI 0.04,0.05; $p < .001$; Table 4.2). Better MWT-B performance (-0.10 dB difference per standard deviation; 95% CI -0.15,-0.05; $p < .001$) and better TMT B performance (-0.12 dB difference per standard deviation; 95% CI -0.18,-0.05; $p < .001$) were associated with better speech in noise performance. We observed no effects for Digit Span Task (-0.02 dB difference per standard deviation; 95% CI -0.07,0.02; $p = .37$) and VLMT delayed recall (-0.05 dB difference per standard deviation; 95% CI -0.10,0.003; $p = .07$). The standardized effect of pure-tone average (ß = .34; 95% CI 0.33,0.35) was four times higher compared to those of MWT-B (ß = -.08; 95% CI -0.12,-0.03) and TMT B (ß = -.09; 95% CI -0.15,-0.03).

Sensitivity Analyses

Performing a complete cases analysis and excluding participants with impaired tympanometric function and hearing aid users did not substantially change the results (Supplementary Material 2, Tables S4.1–S4.3).

Table 4.2. Association of Hearing Sensitivity and Different Cognitive Functions with Central Auditory Processing (n = 1721)

	Age-sex adjusted [a]	**Fully adjusted** [b]
Variable	Speech Reception Threshold difference [dB], (95% CI; p-value)	Speech Reception Threshold difference [dB], (95% CI; p-value)
PTA [dB HL]	0.05 (0.04,0.06; <.001)	0.05 (0.04,0.05; <.001)
MWT-B [*SD*]	-0.10 (-0.15,-0.05; <.001)	-0.10 (-0.15,-0.05; <.001)
TMT B [*SD*]	-0.12 (-0.19,-0.06; <.001)	-0.12 (-0.18,-0.05; <.001)
DS [*SD*]	-0.03 (-0.07,0.02; .25)	-0.02 (-0.07,0.02; .37)
VLMT [*SD*]	-0.05 (-0.10,0.004; .07)	-0.05 (-0.10,0.003; .07)

Note: dB, decibel; PTA, pure-tone average 0.5–4 kilo Hertz; HL, hearing level, MWT-B, Mehrfachwahl-Wortschatz-Intelligenztest; *SD*, standard deviation; TMT B, Trail-making Test B; DS, Digit Span Task; VLMT, Verbal Learning and Memory Test

[a] Multivariable linear regression model adjusted for age (mean centered), age^2, and sex

[b] Multivariable linear regression model adjusted for age (mean centered), age^2, sex, income, education, hypertension, history of cardiovascular disease, diabetes, body mass index, total cholesterol by high-density lipoprotein cholesterol ratio, lipid-lowering medication intake, C-reactive protein level, depression, ototoxic medication intake, smoking, tinnitus, and occupational noise exposure.

4.5 Discussion

The aim of this study was to investigate to what extent hearing sensitivity and different cognitive abilities affect central auditory processing ability across the life span. In line with previous studies, we found that worse hearing sensitivity was associated with worse central auditory processing performance.[32,216] We expand previous findings by showing such an association over the adult life span and across different hearing ability levels. In addition, we investigated the relative effect of different cognitive functions on central auditory processing ability with adjustment for hearing levels across the adult life span. We found that crystallized intelligence and executive functions are relevant for central auditory processing ability while working and long-term memory functions did not show independent effects.

Comparing the effect sizes of hearing sensitivity and the different cognitive functions, we found that the effect of hearing sensitivity was four times higher than the effect of our cognitive measures of crystallized intelligence or executive function. These results are consistent with reports in smaller studies.[216–218] The ability to perceive speech signals might thus play a major role for speech understanding in noise while cognitive functions are supposedly beneficial at a later processing stage, with different involvement of different cognitive functions.

We detected an association between crystallized intelligence and central auditory processing ability. A meta-analysis on four small studies (n = 164) found a pooled association of r = .29 which was, however, not significant.[72] We used the MWT-B as a measure of crystallized intelligence. The test is a vocabulary test which highly relates to language skills and culture-specific knowledge.[207] Due to this relation to vocabulary, comprehension skills, and lexical access, it is conclusive to find an association with central auditory processing.[219] People with better verbal intelligence and lexical knowledge should be more likely to recognize single words and complete the rest of the sentence even if the signal is disrupted through noise.

We showed a positive effect of executive functions on central auditory processing ability that matches previous studies.[72] Executive functions involve control functions such as

control of attention and inhibition[220] and are thought to play a major role in central auditory processing.[221] We assessed executive function with the TMT, which is a measure of attention, speed, and mental flexibility.[222] Selective attention is highly relevant for listeners in situations with competing auditory signals. They need to enhance the representation of a source of interest and simultaneously suppress sources that are not in the focus of attention.[223] Accurate temporal processing, which is also reflected in TMT performance, is as well important for speech understanding.[224] An association between cognitive measures and auditory temporal processing has also previously been reported.[30] Therefore, another possible explanation for this association between speech in noise and TMT performance might be their shared reliance on fast temporal processing.

In our study, working memory did not show an effect on central auditory processing. Working memory capacity is thought to be important for understanding speech in acoustically adverse conditions[225] and many studies have been using working memory tests to examine the association between speech in noise and cognition.[72,216] While Dryden and colleagues showed a medium-sized pooled effect of working memory on speech in noise,[72] Füllgrabe and Rosen did not find a significant effect of working memory on speech in noise in a meta-analysis in young and normal hearers.[226] We used the Digit Span Task which is a measure of the phonemic storage component of working memory that is relevant for maintaining information for a short term.[76] Even though working memory capacity is in principle thought to be limited, it can maintain more information when items are meaningful and relate to each other than if they are unrelated.[227] This was supposedly also the case in our study where we used short meaningful sentences. The working memory capacity of most individuals might be sufficient for the purpose of speech in noise identification[226] and we suppose that previously found associations might reflect other cognitive aspects than working memory storage limits.

Long-term memory functions did not show to be relevant for central auditory processing in our study. Previous studies found an association of long-term or episodic memory with speech in noise.[72] The long-term memory is a fairly permanent repository for information.[228] As our speech in noise task required the immediate recall of the information, it is not surprising that long-term memory functions did not present to have an effect in our

analysis. Previously found associations might have been due to other related cognitive abilities.

Our study has some limitations. First, we were, due to our cross-sectional design, not able to assess the causal relation between hearing sensitivity, cognitive function, and central auditory processing. Further, some of the cognitive tests were conducted with auditory stimulus material (Digit Span Task, Verbal Learning and Memory Test). In order to reduce the possible influence of hearing sensitivity loss on our cognitive measures, participants were using their hearing aids during cognitive testing. Furthermore, there were few hearing impaired participants in our sample and we adjusted for hearing levels in the model.

In conclusion, we showed that hearing sensitivity is most important for central auditory processing. Furthermore, crystallized intelligence and executive functions are relevant for it as opposed to memory functions, which seem less important. Our study facilitates the understanding of age-related hearing loss, which is a major health concern in aging populations. As amplification through hearing aids is in many cases not sufficient to restore central auditory processing,[221] there is growing research on auditory training methods. Since vocabulary skills and semantic knowledge are stable until late in life,[229] future studies could further investigate a beneficial effect of lexical training on central auditory processing impairments.

5 Previous Musical Experience and Cortical Thickness Relate to the Beneficial Effect of Motor Synchronization on Auditory Function

5.1 Abstract

Auditory processing can be enhanced by motor system activity. During auditory-motor synchronization, motor activity guides auditory attention and thus facilitates auditory performance. Previous research on enhanced auditory processing through motor synchronization has been limited to easy tasks with simple stimulus material. Further, the mechanisms and brain regions underlying this synchronization are unclear.

We investigated a beneficial effect of motor synchronization on auditory performance with meaningful auditory material in a complex task. We further assessed how previous musical training and cortical thickness of specific brain regions relate to different aspects of auditory-motor synchronization. We conducted an auditory-motor experiment in 139 adults. The task involved melody discrimination and beat tapping synchronization. Additionally, 68 participants underwent structural magnetic resonance imaging.

We found that melody discrimination improved with better tapping synchrony. However, it was overall worse in the tapping than in the listening only condition. Longer previous musical training and thicker Heschl's gyri were associated with better melody discrimination and better tapping synchrony. The relation of experimental condition with auditory performance depended on structural brain characteristics: Individuals with a thicker left frontopolar cortex performed better when required to tap during the melody discrimination task, whereas individuals with a thinner left frontopolar cortex performed better when listening only.

Our results suggest improved perception of complex auditory stimuli with auditory-motor synchronization. Moreover, prior experience and structural brain differences influence the extent to which an individual can benefit from motor synchronization in complex listening. This could inform future research directed at development of personalized training programs for hearing ability.

5.2 Introduction and Aim

We still lack adequate treatment methods for age-related hearing loss and there is growing interest in the potential to facilitate people's auditory perceptual abilities through training methods.[80]

Even relatively short-term musical training has been associated with changes in brain morphology and physiology subserving auditory processing.[92] The strong auditory-motor interactions that are specific to music are considered one of the driving forces for this neuronal plasticity.[92,111]

Several studies have begun to explore whether auditory-motor synchronization can enhance auditory perception. These studies investigated different aspects of nonverbal auditory processing, namely rhythmic and pitch processing. An immediate effect of motor synchronization on rhythm and timing perception has been shown.[113–115] Furthermore, Morillon *et al.* showed an immediate top-down influence of finger beat tapping on pitch discrimination of random tone sequences.[116]

The proposed mechanism for this is that an interaction between auditory, motor, and attention systems enhances the processing of auditory information.[116,230] The rhythmic motor routine supposedly sharpens sensory representations and facilitates perception of relevant items while it suppresses irrelevant items, enacting auditory 'active sensing'. More specifically, the bottom-up information of the auditory and motor activity may build up a temporal prediction of the sensory event. Additionally, top-down attentional control mechanisms align the rhythmic fluctuations in sensory gain with the rhythm of the incoming sensory input in order to enhance processing.[116] This suggestion is in line with research on the complex interaction of auditory, motor, and top-down cognitive processes, such as attention, in musical performance in general.[111]

It is not entirely clear which brain regions are involved in this type of auditory-motor synchronization. Cerebellum, basal ganglia, and supplementary motor area[111] are involved in timing of movement. Basal ganglia, superior temporal gyrus, premotor cortex, and ventrolateral prefrontal cortex are relevant for beat tapping.[231] A major auditory processing region is the Heschl's gyrus which is relevant for pitch perception[232–234] as well

as retention of rhythmic patterns.[235] While attention networks are thought to involve a widely distributed network of fronto-parietal regions,[236,237] particularly the prefrontal cortex has a major role in top-down attention control mechanisms.[238] The frontopolar cortex has been associated with multi-tasking in a meta-analysis.[239] This region is important for coordination, monitoring, and integration of subgoal processes within the working memory.[240] It specifically mediates the ability to hold goals in mind while exploring and processing secondary goals[241] and re-distributes cognitive control from a current task to other potential goals.[242] We thus hypothesize that auditory (Heschl's gyrus) and premotor regions as well as the frontal poles might be involved in this auditory-motor synchronization.

We aimed to assess a beneficial effect of motor synchronization on auditory performance with meaningful auditory material in a complex auditory task. Furthermore, we investigated whether previous musical training and cortical thickness of specific brain regions relate to auditory, motor, and attention system aspects of auditory-motor synchronization.

5.3 Methods

5.3.1 Study Population

The experiment was performed in 148 participants of the pilot phase of the Rhineland Study. The Rhineland Study is a recently started prospective cohort study. Participants of the pilot study were recruited via newspaper advertisements of local student services. We did not recruit them according to their musical training experience. All participants were healthy, fluent in German, and at least 18 years of age. Approximately half of the pilot subjects were invited to a magnetic resonance imaging (MRI) scan. This invitation to an MRI scan was unrelated to any of the criteria of the experiment.

Ethical approval was obtained from the ethics committee of the University of Bonn, Medical Faculty .All participants gave written informed consent in accordance with the Declaration of Helsinki.

5.3.2 Study Procedure

For the present study, participants performed a melody experiment and answered a short questionnaire on musical background. Moreover, MRI scans were available for 72 of those participants.

5.3.3 Melody Experiment

In the melody experiment, the main task was a simple melody condition where participants had to decide by button press whether or not two melodies in a row were the same.[243,244] In half of the trials the pitch of a single note was changed by up to ±5 semitones (median of 2 semitones). This change maintained the key and the melodic contour (the order of upward and downward pitch movement in a melody without regard to magnitude) of the melody. The melody stimuli were 5 to 13 notes in duration, low pass-filtered harmonic tones with pitches between C4 and E6. All notes were 320 ms in duration, equivalent to eighth notes at a tempo of 93.75 beats per minute, that is, all melodies had an isochronous rhythm. Varying the number of notes among trials ensured a sufficient range of difficulty and sensitivity across the full range of musical experience in our sample.[243,244] The task was conducted on a Samsung Galaxy note 10.1 2014 edition with Sennheiser HD 201 headphones. All stimuli were presented at a comfortable hearing level.

We presented the melody task in two experimental conditions (Figure 2). In half of the trials the participant merely listened to the melodies, whereas in the other half of the trials they tapped along to the beat of the melody with the left index finger. Since neuronal activity related to pitch discrimination is right-lateralized,[245] and since we wanted to maximize the potential influence of motor synchronization, we asked participants to tap with their left index finger in order to enhance neuronal activity in the right-hemispheric network.

In order to introduce participants to the beat before the start of the first melody, all trials started with four beats presented in a wooden sticks sound. The beat also continued during the interval between the first and second melody, bridging the two melodies with four beats. In the tapping condition, participants were instructed to start tapping on the

first beats and to continue throughout the whole trial, including the interval between the two melodies. Before the experiment, participants practiced tapping to the beat for 30 s and performed four exercise trials of the tapping condition. We divided 72 trials in four blocks, with tapping and listening conditions alternating twice. We used four different versions of trial orders. Versions and order of conditions were counterbalanced across participants. Total task duration was approximately 18 minutes.

Melody discrimination performance (MDP) was computed as percent correct answers on melody discrimination task. We computed this sum score across all trials as well as separate scores for the tapping and listening conditions.

Additionally, we computed a score of tapping performance for each melody trial, the sensorimotor simultaneity index (SSI). To compute the SSI, we first established a theoretical reference beat corresponding to occurrences of the target taps each 320ms along the sequence of tones of the trial. We corrected for a possible delay in the recording of the motor acts by extracting the motor-tracking sequence and aligning it to the theoretical reference beat number one so as to minimize the trial-averaged delay between the two sequences.[116] On each trial, we excluded the first four beats before the start of the melody from the estimation of the SSI since they served as introductory phase to find the beat. SSI was defined as the mean absolute temporal distance between target taps and actual taps and describes the ability to closely match the tone onset. A higher score refers to worse tapping ability. We used both trial-by-trial SSI scores and a sum score of mean SSI across all tapping trials per participant in the statistical analyses. In order to ensure valid estimation of tapping performance per trial, trials with more than [mean number of taps + three standard deviations] missing taps per melody (equivalent to 37% of taps per melody) were excluded. After this step, if more than 10% of trials per participant were missing, the participant was excluded to ensure valid estimation of tapping performance per participant.

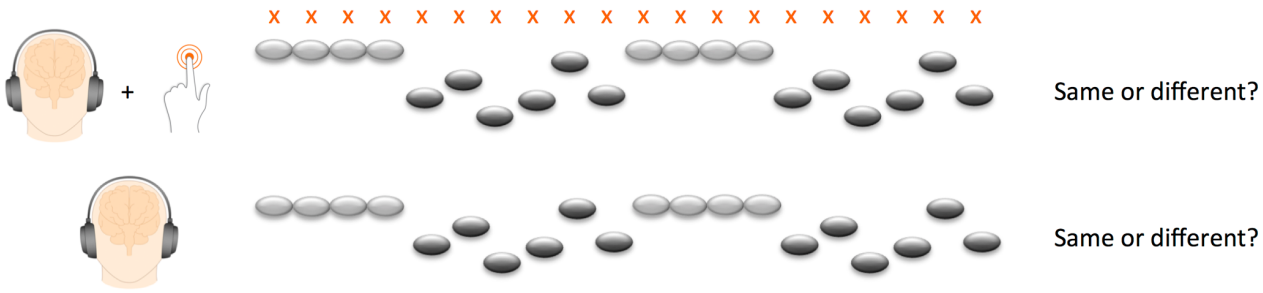

Figure 2. Melody Experiment Paradigm.

5.3.4 Other Variables

The following data were collected using a self-report questionnaire: sex, age, handedness, and history of musical training, which included years of musical training and starting age of musical training. Starting age was missing for one individual who therefore was omitted from analyses including starting age as a variable.

5.3.5 Magnetic Resonance Image Acquisition and Processing

MRI sessions were scheduled on the same day as the behavioral examinations. T1 and FLAIR scans were acquired alongside other sequences of the Rhineland Study MRI pilot protocol within a 50 minutes session on a Siemens 3 Tesla scanner (Siemens, Prisma Magnetom, Erlangen, Germany). Both structural images were acquired with whole brain coverage and an isotropic 1x1x1 mm resolution with an MPRAGE sequence (field of view: 256 x 256 mm, repetition time: 2530 ms, echo time: 2.83 ms, flip angle: 7.0°, acquisition time: 4:57 min) and a FLAIR sequence (field of view: 256 x 256 mm, repetition time: 5000 ms, echo time: 393 ms, flip angle: 120°, acquisition time: 4:42 min). We processed the data according to the recommended surface-based analysis stream for cortical surface segmentation in FreeSurfer Version 5.3[246,247] including registration to the MNI305 atlas, skull stripping, and classification of voxels as white and non-white matter. For each hemisphere separately, the algorithm computes surfaces to separate white from gray matter (white surface), and gray matter from cerebrospinal fluid (pial surface). FLAIR data were used to improve surface estimates. Finally, cortical thickness estimates

were generated from the distance between white and pial surface. Then, based on the Desikan atlas,[248] we extracted average cortical thickness values for each individual for the following regions of interest (ROIs): right and left transverse temporal cortex (Heschl's gyrus), right superior frontal cortex (including premotor areas), and right and left frontal pole. We further extracted the estimated intracranial volume.[249]

5.3.6 Statistical Analyses

We compared sample characteristics between the total sample and the subset with MRI using chi-squared tests and univariate analyses of variance.

To check the quality of our designed experiment, we examined several aspects: possible performance differences due to the experimental version, performance increase or decrease over the four experimental blocks in MDP due to learning or fatigue respectively using univariate analyses of variance, and the reliability of MDP using the formula $r_{\text{Spearman-Brown}} = \frac{2 \times r}{1+r}$ with r = Pearson correlation of test halves.[250]

We investigated the effect of motor synchronization on auditory task performance on a trial and on a subject level. First, we investigated the effect of SSI on the probability to give a correct melody discrimination answer on each trial. Here, SSI varies across trials for each participant. We used a generalized linear mixed model to account for repeated measures. We defined SSI per trial as independent variable and correctness (0 versus 1) of the melody discrimination answer of the respective trial as dependent variable. We adjusted for random effects of trial and participant and reran the model with additional adjustment for years of musical training and trial length. Second, we tested the effects of SSI and of experimental condition (tapping versus listening) on MDP. Here we used average SSI across all tapping trials as index for rhythmic synchronization skills that vary across participants. We used a linear mixed-effects model with average SSI and the experimental condition (tapping versus listening) as independent variables and MDP as dependent variable. We controlled for random effect of participant and reran the model with adjustment for years of musical training.

To examine whether musical training relates to the auditory component or the motor component of auditory-motor synchronization, we used linear regression models with years of musical training and starting age of musical training as independent variables and MDP or SSI as dependent variables.

In the MRI subsample, we then investigated whether cortical thickness in Heschl's gyrus or right superior frontal cortex were related to the auditory or motor component of auditory-motor synchronization with linear regression analyses. We used models with Heschl's gyrus (left and right hemisphere separately) cortical thickness as independent and MDP or SSI as dependent variable. Furthermore, we used a model with right superior frontal cortical thickness as independent and SSI as dependent variable. We adjusted all models for intracranial volume and also reran the analyses with additional adjustment for musical training years.

Finally, we assessed whether the effect of motor synchronization on auditory function was dependent on frontopolar cortical thickness. We first plotted the difference in MDP between the experiment conditions (tapping and listening) as a function of frontopolar cortical thickness. To further examine this relation, we used a linear mixed-effects model with main effects of frontopolar cortex thickness and experiment condition (tapping versus listening) as well as the interaction between experiment condition and frontopolar cortex thickness as independent variables and MDP as dependent variable. We corrected for intracranial volume, years of musical training, and random effect of participant. To investigate a possible influence of handedness, we assessed whether these effects were consistent in right-handed individuals only.

For all linear models we winsorized extreme values of SSI (defined as values deviating more than three standard deviations from population mean). We log-transformed highly skewed data on starting age of musical training and z-standardized the cortical thickness values of the ROIs. The threshold for statistical significance was set at $\alpha < .05$.

Statistical procedures were performed in Matlab Version R2015b[251] and R Version 1.0.44[211] with packages dplyr,[212] tidyr,[252] moments,[253] car,[254] lmertest,[255] lme4,[256] and ggplot2.[257]

5.4 Results

Of the 148 participants who conducted the melody experiment we had to exclude one participant with only 22.2% correct answers in the last block, assuming concentration issues or failure to follow instructions, and further 8 participants because of missing data in SSI. Of the remaining 139 participants MRI data were available for 68 subjects. Table 5.1 presents the descriptive characteristics of the participants of the total sample and the MRI subsample. Samples did not significantly differ in any of the reported characteristics ($p > .25$). For those participants who received musical training (n = 88) there was a wide range of years (between 1 and 16) and starting age (4 to 21) of musical training. On average, participants answered correctly in 70.1% (SD = 9.5%) of the trials and their taps deviated 32.7 ms (SD = 14.9 ms) from tone onset.

MDP showed an acceptable split-half reliability (r = .77). There was neither a significant effect of experimental version on MDP nor a significant performance increase or decrease over the four blocks ($p > .15$).

Table 5.1. Characteristics of Participants of Total Analytic Sample (n = 139) and MRI Subsample (n = 68) of the Student Pilot Population of the Rhineland Study

Characteristic	Total sample	MRI subsample
Age, yrs, *M (SD)*	25.4 (4.4)	24.7 (4.0)
Women, *n (%)*	83 (59.7)	42 (61.8)
Right handedness, *n (%)*	124 (89.2)	59 (86.8)
Musical training, *n (%)*	88 (63.3)	46 (67.6)
Musical training, yrs, *M (SD)*	4.3 (4.8)	4.6 (4.7)
SA of musical training, yrs, *M (SD)*	8.4 (3.3)	8.1 (3.2)
Experiment Performance		
MDP total, % correct, *M (SD)*	70.1 (9.5)	71.3 (8.8)
MDP listening, % correct, *M (SD)*	71.0 (11.0)	72.2 (10.5)
MDP tapping, % correct, *M (SD)*	69.1 (10.6)	70.3 (9.7)
SSI, ms, *M (SD)*	32.7 (14.9)	31.7 (14.1)
Cortical Thickness		
Right HG thickness, mm, *M (SD)*	-	2.6 (0.2)
Left HG thickness, mm, *M (SD)*	-	2.5 (0.2)
Left SFC thickness, mm, *M (SD)*	-	2.8 (0.1)
Right FPC thickness, mm, *M (SD)*	-	2.8 (0.2)
Left FPC thickness, mm, *M (SD)*	-	2.8 (0.2)

Note: *M*, mean; *SD*, standard deviation; SA, starting age; MDP, melody discrimination performance; SSI, sensorimotor simultaneity index; HG, Heschl's gyrus; SFC, superior frontal cortex; FPC, frontopolar cortex.

5.4.1 Effect of Tapping Performance on Melody Discrimination

Analyses on Trial Level

More precise tapping in a specific trial increased the probability of a correct answer in the melody discrimination task in the same trial (-0.005, t = -2.81, p = .005). The average SSI for incorrectly answered melody discrimination items was higher (M = 34.7, SD = 21.3) than for correctly answered items (M = 31.8, SD = 20.6). Adjusting for years of musical training and trial length did not substantially change the results (-0.005, t = -2.06, p = .04).

Analyses on Subject Level

On average participants performed worse in the tapping condition (M = 69.1, SD = 10.6) than during the listening only condition (M = 71.0, SD = 11.0; -1.87 mean difference of tapping and listening, t = -2.12, p = .04). However, participants who tapped more precisely performed better on the melody discrimination task (-0.25% difference per ms; t = -4.99; p < .001). Adjusting for years of musical training slightly decreased this effect (-0.18% difference per ms; t = -3.81; p < .001).

5.4.2 Effects of Musical Training on Melody Discrimination and Tapping Performance

Longer musical training was associated with better MDP (Table 5.2). Among musicians, earlier in life start of musical training tended to be related to better melody discrimination performance. However, in our sample starting age was strongly correlated with duration of musical training (r [Pearson] = -.38, p < .001). When we entered both variables simultaneously in the model, the effect of years of musical training hardly changed but the effect of starting age largely disappeared (Table 5.2). Furthermore, longer musical training was associated with a better tapping performance (smaller SSI; Table 5.2). Starting age of musical training showed no significant effect (Table 5.2).

5.4.3 Effects of Cortical Thickness on Melody Discrimination and Tapping Performance

In the MRI subgroup, a thicker right but not left Heschl's gyrus was associated with better MDP (Table 5.3). When we adjusted for duration of musical training, the effect size of right Heschl's gyrus became slightly smaller and only borderline statistically significant (Table 5.3). A thicker left and right Heschl's gyrus were also associated with better tapping performance (Table 5.3). When additionally controlling for years of musical training, the effect sizes slightly decreased and only the right Heschl's gyrus remained significantly associated with tapping performance (Table 5.3). We did not find a significant association of right superior frontal cortical thickness and SSI (Table 5.3).

Table 5.2. Effects of Years of Musical Training and Starting Age of Musical Training on Melody Discrimination Performance and Tapping Performance in the Total Analytic Sample

Model	Determinant	Difference MDP [%] [a]	95% CI		*t*	*p*	Difference SSI [ms] [a]	95% CI		*t*	*p*
1	**Musical training [yr]**	0.89	0.59	1.19	5.84	<.001	-0.88	-1.39	-0.38	-3.44	<.001
2	**SA of musical training [log(yr)]**	-4.97	-10.44	0.49	-1.81	.07	2.80	-5.00	10.61	0.71	.48
3	**Musical training [yr]**	0.76	0.30	1.21	3.30	.001	-	-	-	-	-
	SA of musical training [log(yr)]	-1.47	-7.06	4.11	-0.52	.60	-	-	-	-	-

Note: MDP, melody discrimination performance; SA, starting age; SSI, sensorimotor simultaneity index.

[a] Linear regression models on MDP and SSI were independently tested.

Table 5.3. Effects of Heschl's Gyrus Cortical Thickness on Melody Discrimination and Effects of Heschl's Gyrus Cortical Thickness and Right Superior Frontal Cortex on Tapping Performance in the MRI Subsample

Model	Determinant	Difference MDP [%] [a]	95% CI		*t*	*p*	Difference SSI [ms] [a]	95% CI		*t*	*p*
1	**Right HG CT [*SD*]**	2.44	0.37	4.51	2.35	.02	-3.65	-7.02	-0.29	-2.17	.03
2	**Right HG CT [*SD*]**	1.93	-0.10	3.96	1.90	.06	-3.47	-6.92	-0.02	-2.01	.049
	Musical training [yr]	0.55	0.11	0.99	2.52	.01	-0.20	-0.94	0.55	-0.53	.60
3	**Left HG CT [*SD*]**	0.57	-1.64	2.77	0.51	.61	-3.71	-7.15	-0.27	-2.15	.03
4	**Left HG CT [*SD*]**	-0.40	-2.60	1.80	-0.37	.72	-3.54	-7.18	0.10	-1.94	.06
	Musical training [yr]	0.66	0.20	1.12	2.85	.01	-0.11	-0.88	0.65	-0.30	.77
5	**Right SFC CT [*SD*]**	-	-	-	-	-	-0.53	-4.01	2.94	-0.31	.76

Note: MDP, melody discrimination performance; SSI, sensorimotor simultaneity index; HG, Heschl's gyrus; CT, Cortical Thickness; *SD*, standard deviation; SFC, superior frontal cortex.

[a] Linear regression models on MDP and SSI were independently tested; all models were adjusted for intracranial volume.

5.4.4 Moderating Effect of Frontal Pole Cortical Thickness on Melody Discrimination

In the MRI subgroup, the effect of condition (tapping versus listening) on MDP was comparable to the effect in the larger behavioral sample (-1.84 mean difference between tapping and listening, t = -1.59, p = .12) i.e. overall performance was worse during tapping than during listening only. This relation depended on frontal pole cortical thickness with individuals with thinner frontal poles showing worse performance during tapping than during listening, and individuals with thicker frontal poles showing better melody discrimination when tapping (Figure 3). The interaction of frontal pole cortical thickness and condition (tapping versus listening) on MDP was statistically significant for the left frontal pole (2.5% increase in the difference between tapping and listening condition per 1 *SD* increase in frontal pole thickness, t = 2.15, p = .04), but not for the right frontal pole (1.35% increase in the difference between tapping and listening condition per 1 *SD* increase in frontal pole thickness, t = 1.14, p = .26). There were no substantial differences in any of the effects in the right-handed individuals only.

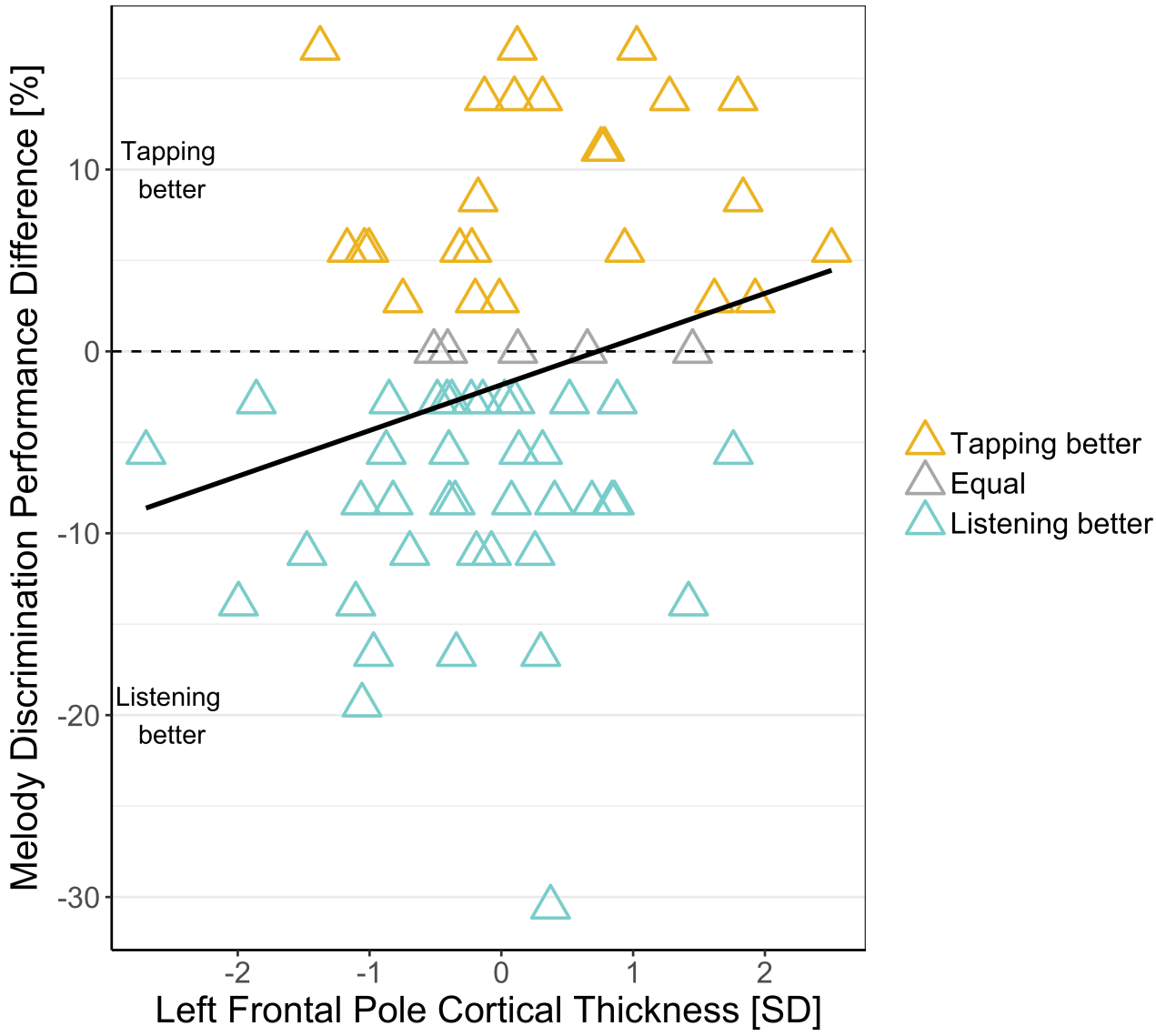

Figure 3. Association of the Difference Between Melody Discrimination Performance in Tapping and Listening Condition with Left Frontal Pole Cortical Thickness.

5.5 Discussion

We found a beneficial effect of motor synchronization on auditory processing of meaningful material in a challenging discrimination task. However, although melody discrimination improved with better tapping synchrony, it was worse in the tapping than the listening only condition. Longer musical training and a thicker Heschl's gyrus were associated with better melody discrimination (auditory component) and with better tapping synchrony (motor component). Frontal brain structures modified the association between condition and auditory performance in that individuals with a thicker left frontopolar cortex performed better when they were required to tap during the melody discrimination task, whereas individuals with a thinner left frontopolar cortex performed better when they were listening only.

We designed an experiment by adding a tapping task to an existing auditory discrimination task. Our combined task showed a good split-half reliability of our main outcome score MDP. The mean MDP (*M* = 70%) was slightly lower compared to a previous experiment (*M* = 76%).[243] This could be due to sample differences or because adding the tapping component increased the global difficulty level. However, there were no bottom or ceiling effects according to the distributions of the data, and neither did we find any effects of fatigue in MDP during the course of the task. We also could not find effects of experiment version on MDP.

5.5.1 Effect of Motor Synchronization on Auditory Processing

In order to understand the effect of synchronized motor action on auditory task performance, we analyzed the effect of tapping accuracy on melody discrimination both at trial level and subject level. On both levels, variations in the tapping performance are meaningful. At the trial level, the tapping score represents dynamic changes in the tapping performance as a state, which possibly depends on other variables such as situational attention and practice effects. At the subject level, the tapping score represents the overall motor synchronization performance as a trait, which varies across individuals, and might be influenced by the training background of the person.

In line with our hypothesis, we found that tapping improved melody discrimination on a trial-by-trial basis, after controlling for the amount of musical training. Our findings are in line and extend the results of Morillon *et al*. about a facilitation of auditory perception by top-down motor control of tapping.[116] The stimuli used in Morillon's study were random tone sequences that did not follow musical rules, and the judgment required was about average pitch of the tones. Our study used meaningful and more complex auditory stimuli. In our analyses, we excluded effects of short-term training or fatigue, stimulus-specific effects such as length of melody, and musical training. Therefore, Morillon's suggestions for active sensing as possible mechanism underlying this effect are plausible for our melody stimuli, too.

On the subject level, the benefit of tapping for auditory discrimination was not consistent across participants. Overall, the performance in the tapping condition was worse than in the listening only condition, and this was an unexpected finding. Nevertheless, participants who tapped more precisely performed better on the melody discrimination task, regardless of musical training. That is, some participants seemed to benefit from the tapping, whereas in others tapping seemed to harm auditory discrimination performance. A possible explanation is that our task can be conceived as two parallel, and possibly competing tasks. Morillon and colleagues[116] showed an overall better performance in pitch discrimination in the motor-tracking condition in contrast to the listening only condition. Compared to the task used by Morillon our reference beat was twice as fast (320 ms vs. 667 ms). Besides, most participants tapped with their non-dominant left hand, which increased difficulty and might have reduced cognitive resources available for melody discrimination. Our melodies were shorter than in previous studies and lengths of the melodies varied, adding an element of unpredictability. On any given trial, participants did not know how long the melody will be and how long they will synchronize. This might have rendered our tapping task more challenging, which might have increased the dual task effort and might have thus reduced the beneficial effect of tapping compared to the previous findings.

5.5.2 Effects of Musical Training and Cortical Thickness on Melody Discrimination

In order to understand the auditory component of the auditory-motor-interaction, we examined the effect of musical training and Heschl's gyrus cortical thickness on MDP. We replicated previous findings that more musical training is associated with better melody discrimination.[243] In addition, we found that the younger people start with musical training the better their melody discrimination is, in line with previous results.[243] However, musical training years and starting age were highly correlated in our sample. When we assessed them jointly, only years of musical training remained associated with melody discrimination performance.

Additionally, we showed an association of right Heschl's gyrus cortical thickness and melody discrimination performance, which is in line with previous studies showing the Heschl's gyrus being relevant for pitch discrimination.[232–234,243] When we included musical training in the model, the effect size of Heschl's gyrus cortical thickness decreased and was no longer statistically significant. This pattern is consistent with previous observations.[243] Our finding of an effect in the right but not the left Heschl's gyrus is consistent with a right-hemisphere advantage for pitch discrimination of the Heschl's gyrus.[245]

5.5.3 Effects of Musical Training and Cortical Thickness on Tapping Performance

We showed a positive effect of musical training on tapping accuracy, with more training showing less deviation from tone onset. This finding is in line with previous studies that showed that musical training can improve rhythmic perception and production.[258–260] For the starting age of musical training, we did not find a significant association with tapping accuracy.

A thicker Heschl's gyrus was associated with more precise tapping, also when controlling for years of musical training. This is in line with a previous lesion study showing the Heschl's gyrus to be necessary for retention and reproduction of a precise analogue representation of auditory rhythmic patterns.[235] We extend previous research by showing an association of Heschl's gyrus cortical thickness and rhythmic motor tapping, revealing its role in motor synchronization.

Previous studies report about the importance of the premotor cortex for rhythmic tapping.[231,261] In our experiment participants were instructed to tap with their left index finger, thus we hypothesized to find an association of the right superior frontal cortical thickness and tapping accuracy, which we did not find. One possible explanation is, that the superior frontal cortex region we extracted using the Desikan atlas[248] is a large brain region which codes for various different brain functions and not solely for (finger) motor control. One way to improve statistical power and specificity of analyses in following studies could be using ROIs based on functional activations during the same task rather than anatomically defined ROIs. An additional limitation of our study is that the image contrast in subcortical regions was not sufficient to evaluate further effects of subcortical regions.

5.5.4 Moderating Effect of Frontal Pole Cortical Thickness on Melody Discrimination

We found that the effect of condition on melody discrimination was dependent on frontal pole cortical thickness: Individuals with thinner frontal poles showed worse performance during tapping than during listening, while individuals with thicker frontal poles showed better auditory discrimination while tapping compared to listening. We had expected that auditory-motor synchronization would enhance melody discrimination ability, but this relationship was only true in individuals with thicker frontal poles. One possible way to interpret this result is that tapping in our task did not always support auditory discrimination, but that the two tasks (tapping and auditory discrimination) could be seen as two competing tasks. In this case, our combined task required multi-tasking. This fits with previous reports of the involvement of the frontal pole in multi-tasking.[239–241] Those individuals with a thicker frontal pole supposedly have more capacity in a multi-tasking brain region. This might enhance their ability to conduct two tasks at a time with fewer costs, and thus they show improved auditory performance when additionally tapping. Our results especially fit the argumentation, that the frontal pole is important for keeping in mind one main goal while pursuing other tasks.[241] Our participants had to decide whether two melodies in a row where the same or not, which could be considered the main goal, and meanwhile, in half of the trials, to tap along with the beat. Although we found the direction of effect for both the left and right frontal poles, the effect size was larger,

and only statistically significant, for the left frontal pole. Whether this difference is real or due to our relatively small sample size needs to be assessed in future studies.

Our results support the simultaneous involvement of two different mechanisms – the alignment of movement with sensory input and the alignment of temporal attention – in the effect of motor synchronization on auditory function.[116] People can benefit from tapping, when they tap accurately enough to align their motor processing with the auditory input. Additionally, they need to align their attention to benefit from this sensory enhancement. According to our findings the Heschl's gyrus might be important for auditory and motor processing and one of the neural correlates of the attentional process might be the frontal pole. A role of additional structures in the fronto-parietal attention network[236,237] and subcortical motor regions[111,231] is likely and could be explored in future imaging studies, e.g. using functional MRI.

In conclusion, we found a beneficial effect of motor synchronization on auditory processing of meaningful material in a challenging discrimination task. This generalizes the beneficial effect and points out a possible usefulness of such interventions for clinical applications. In clinical applications, so far, synchronous motor movements have been mainly used to enhance speech production rather than processing, e.g. in melodic intonation therapy for stroke.[262] It remains to be assessed whether the benefits of auditory-motor training transfer to daily life hearing skills. One next step might be to extend this motor enhancement of auditory processing further to non-musical processing such as discrimination of speech sounds. Moreover, we disentangled multiple influences on auditory-motor synchronization. We demonstrated the effects of previous experience in musical training and anatomical variability of relevant brain regions on auditory and motor aspects of task performance. We found that structural brain differences might influence the extent to which an individual can benefit from motor synchronization in a complex listening task. Further studies will have to corroborate these findings. If confirmed, our findings could have important implications for the development of personalized auditory-motor training programs to enhance hearing ability.

6 Associations of Hearing Sensitivity, Central Auditory Processing, and Cognition over Time in Aging Adults

6.1 Abstract

Age-related hearing loss (impairment in hearing sensitivity and/or central auditory processing) and cognitive decline are common co-occurring impairments in the elderly. Their relation in the process of aging is still insufficiently understood. We aim to assess the temporal relations of decline in hearing sensitivity, central auditory processing, and cognition.

This study included 1274 Beaver Dam Offspring Study participants who participated in three examinations (baseline, 5-year, and 10-year follow-up). We assessed hearing sensitivity through pure-tone audiometry (PTA of 0.5, 1, 2, 4 kHz of the better ear), central auditory processing as word recognition in competing message (WRCM) using the Northwestern University 6 word list in the better ear, and cognition through TMT performance. Linear mixed-effects models and linear regression models were used to determine associations over time and to what extent these measures influence each other over time.

The decline between all functions was associated over time with the strongest relations between PTA and WRCM. The effect of baseline PTA on WRCM ten years later (standardized ß = -.30) was almost twice as big as the effect of baseline WRCM on PTA ten years later (standardized ß = -.18). The effect of baseline WRCM on TMT ten years later and vice versa were small (standardized ß = -.05). No directional relationship between PTA and TMT was identified (standardized ß ≤ -.02).

While hearing sensitivity might affect higher-order central auditory processing, the associations between hearing and cognition appear bidirectional and weak. We need to be cautious before inferring a causal effect of hearing on cognition.

6.2 Introduction and Aim

The association of hearing impairment and cognitive function has gained increasing attention over the last years. While an association between hearing impairment and cognition has repeatedly been shown,[15,16] the direction of this association and underlying mechanisms are not understood, due to limitations in existing prospective studies.

First, the majority of longitudinal studies were conducted in older adults. Studies on early changes in midlife are scarce.[263] Second, except for one,[264] studies did not assess the temporality of events and compare the strengths of effects going from hearing to cognition and from cognition to hearing. Finally, most studies investigated audiometrically assessed hearing while central auditory processing has been neglected.

In order to investigate the complex interplay of decline in different hearing functions and cognition (Figure 4), we conducted the following study. The aim of our study was to determine the longitudinal associations of (1) hearing sensitivity and central auditory processing, (2) central auditory processing and cognition, and (3) hearing sensitivity and cognition, in middle-aged adults.

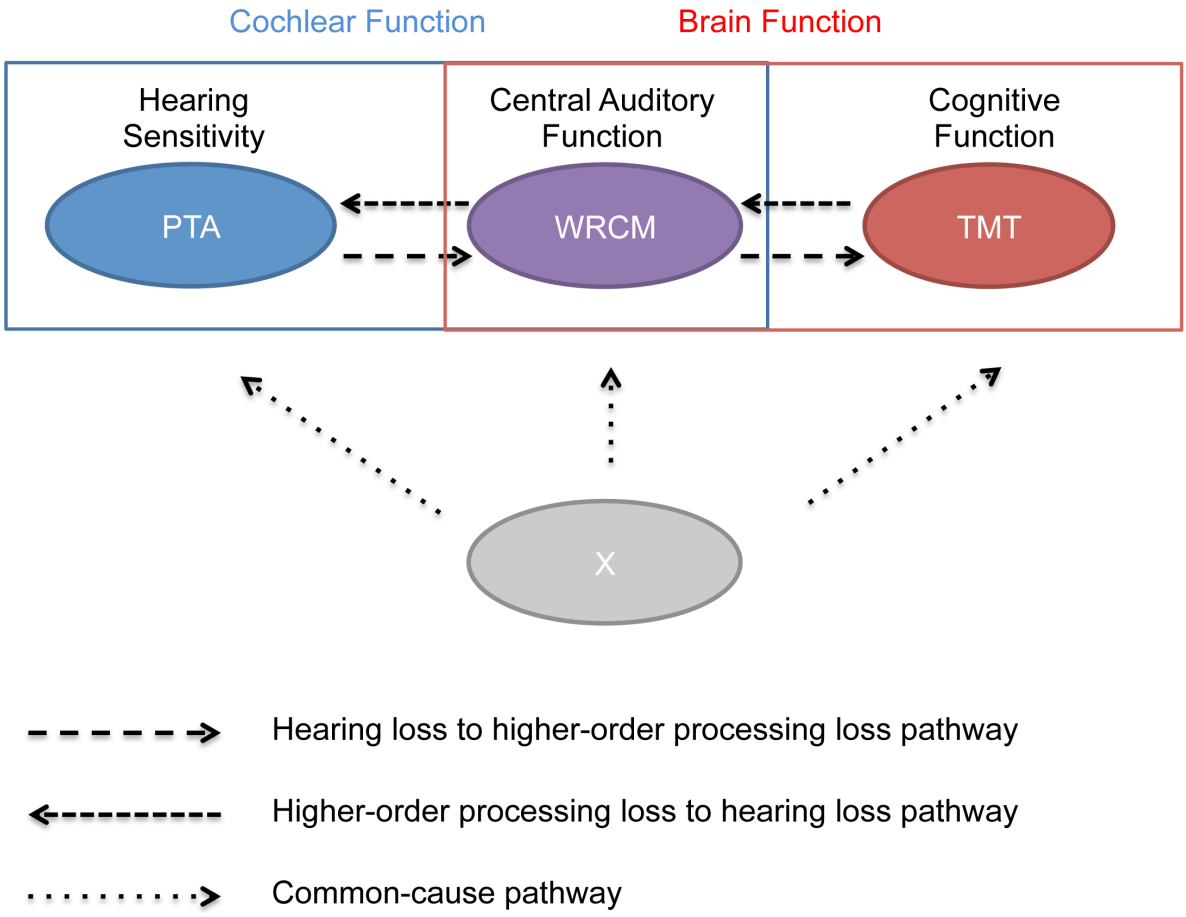

Figure 4. Theoretical Background of the Association between Hearing and Cognition.

6.3 Methods

6.3.1 Study Population

This study involves participants of the Beaver Dam Offspring Study, which is a prospective cohort study of aging. The adult offspring of the population-based Epidemiology of Hearing Loss Study participants were eligible for the Beaver Dam Offspring Study. In the baseline examination (conducted 2005–2008) 3298 subjects (aged 21 to 84 years) participated.[150] The 5-year follow-up (2010–2013) showed a participation rate greater than 80%[128] and the 10-year follow-up (2015–2017) a participation rate of 75% of baseline participants. Participation rate in the 10-year follow-up among those who participated in

the 5-year follow-up was 86%. Approval for this research was obtained from the Health Sciences Institutional Review Board of the University of Wisconsin and written informed consent was obtained from all participants before each examination.

Participants were eligible for inclusion in these analyses, if they were examined at all three examination waves. We excluded participants who: were less than the age of 30 years at baseline, had probable cognitive impairment at baseline, reported the onset of hearing loss before the age of 20 years, or had ever undergone tympanoplasty, mastoidectomy, and/or stapedectomy.

6.3.2 Measurements

Examinations listed below were performed in all three waves. Each examination included tests of hearing, vision, olfaction, cognition, and numerous other measures, a blood draw, and questionnaires about medication intake, medical history, lifestyle, behavior, and hearing health history.[178] We asked participants about any ear surgeries, their hearing aid use, self-assessed hearing impairment, and the age of onset of the hearing loss, if any. Some participants opted to complete only the questionnaire.

Auditory Assessment

Audiometric testing was conducted in either a sound-treated booth or with insert earphones and followed American National Standards Institute standards for equipment.[265,266]

Pure-tone air and bone conduction audiometry was conducted following the American Speech-Language-Hearing Association guidelines.[267] Pure-tone air conduction thresholds were obtained at 0.5, 1, 2, 3, 4, 6, and 8 kHz, and bone conduction thresholds at 0.5 and 2 kHz for both ears using clinical audiometers with TDH-50P earphones and ER-3A insert earphones (in cases of probable ear-canal collapse or if testing outside the booth). When necessary, masking was done. Conductive hearing loss was defined as an air-bone gap of 15 dB or greater at 0.5 or 2 kHz. The pure-tone average at 0.5, 1, 2, and 4 kHz in the better ear was calculated and used as a measure of hearing sensitivity. Higher scores indicate poorer performance.

Word recognition in competing message was assessed with the Northwestern University Auditory Test Number 6.[29,268] In this test 25 words were presented with a single female voice to the better ear at 36 dB HL above the individual's threshold at 2 kHz. If thresholds at 2 kHz were equal in both ears, testing was performed in the right ear. The competing message (single male speaker) was added at a level 8 dB HL below the female speaker's level in that same ear.[29] We used the percentage of correctly repeated target words in competing message to measure central auditory processing. Higher scores indicate better performances.

Cognitive Assessment

The paper-pencil TMT versions A (consecutive numbers are to be connected) and B (alternating consecutive numbers and letters are to be connected) were administered.[205] Main outcome is completion time in seconds. Longer durations indicate poorer performance. Inability to complete the test in allotted five minutes resulted in a score of 301 seconds. The TMT is a measure of attention, speed, and mental flexibility. Since perceptual processing speed has been shown to change throughout the whole adult life span in longitudinal studies,[229] TMT performance should be a good marker of early cognitive change. TMT B is considered more complex and makes greater demands on perceptual processes and motor speed than TMT A.[222] Therefore, we used TMT B as a measure of cognitive function.

Further, we conducted the Mini-Mental-State Examination (MMSE) in participants aged 50 years and older.[269] Probable cognitive impairment was defined as an MMSE score of less than 24 and/or a history of diagnosed dementia.

In these analyses, data from the TMT and MMSE were included as they were repeated in each of the three examinations.

6.3.3 Other Variables

We evaluated several baseline covariates as potential confounders. Age, sex, race, income, education, history of cardiovascular disease (defined as history of stroke, myocardial infarction, angina, congestive heart failure, transient ischemic attack, peripheral

vascular disease, thrombosis, angioplasty or a stent operation, coronary bypass, and/or carotid arteries surgery), smoking history, history of chemotherapy, years of musical training (played at least once a week), occupational noise exposure (defined as ever holding a full-time job that required speaking in a raised voice or louder to be heard when within two feet from another person or having military service with noise exposure), history of heavy drinking (defined as drinking more than four alcoholic beverages per day), regular exercise (at least once a week long enough to work up a sweat), and medication (including loop diuretics) intake were assessed using self-report. From blood samples, we assessed non-high-density lipoprotein cholesterol levels,[150] glycated hemoglobin levels, and inflammatory marker levels of high-sensitivity C-reactive protein (hsCRP) and interleukin-6 (IL-6).[270] We used carotid artery ultrasound scans to measure intima-media thickness.[271] Body mass index (weight in kilograms divided by height in meters squared) was calculated. Hypertension was defined as systolic blood pressure >139 mmHg and/or diastolic blood pressure >89 mmHg and/or use of antihypertensive drugs, diabetes as history of diabetes diagnosis and/or glycated hemoglobin ≥ 6.5, and depression as taking antidepressants and/or having depressive symptoms (using the Center for Epidemiological Studies – Depression questionnaire).

6.3.4 Statistical Analyses

We assessed the strength of associations of (1) hearing sensitivity (PTA) and central auditory processing (WRCM), (2) central auditory processing and cognition (TMT), and (3) hearing sensitivity and cognition over ten years.

For each relationship, we first used linear mixed-effects models to quantify the strength of the association using all data from baseline, 5-year, and 10-year follow-up. Each model included age (mean centered at baseline) as the timescale variable and covariates of baseline age in decades (to account for different baseline hazards of different age groups) and sex. The first model included WRCM as dependent variable and PTA and the interaction of PTA with age as independent variables. The second model included TMT as dependent variable and WRCM and the interaction of WRCM with age as independent variables and the third model included TMT as dependent variable and PTA and the interaction of PTA with age as independent variables. As data from each

study wave were used in these models, each included term was allowed to vary over time, with the exception of age at baseline in decades and sex. A random intercept and a random slope were also included in each linear mixed-effects model (Supplementary Material 3, Equations 1–3). We repeated the models with including further potential confounding variables.

Next, we used multivariable linear regression models to quantify the strength of the association of each variable at baseline (hearing sensitivity/ central auditory processing/ cognition) with each other variable at the 10-year follow-up time point. Each model was adjusted for age, sex, and dependent variable at baseline (performance in quartiles). We repeated the models including further potential confounding variables. The strengths of the standardized associations from each linear model were compared to gauge the directionality of effects.

Data Preparation and Confounding

We log-transformed and z-standardized (with baseline values) TMT. To protect personal health information in light of a small number of participants in the oldest age group, ages of the oldest participants were reported as 75+ at baseline, 80+ at 5-year follow-up, and 84+ at 10-year follow-up.

To evaluate confounding, age- and sex-adjusted models were computed for each potential individual confounder. Variables that were associated with either overall or change in performance of both measures of interest (PTA and WRCM; WRCM and TMT; PTA and TMT) were used as covariates. Resulting covariates for all models were income, education, regular exercise, hsCRP, IL-6, history of cardiovascular disease, smoking, intima-media thickness, occupational noise exposure, and loop diuretics intake. Further covariates for PTA and TMT models were body mass index, history of heavy drinking, depression, years of musical training, diabetes, and non-high-density lipoprotein cholesterol levels, and for PTA and WRCM models chemotherapy.

Sensitivity Analyses

To evaluate if associations in non hearing aid users and in participants without conductive hearing loss were consistent with the observed effects in the whole cohort, models were repeated excluding hearing aid users (n = 53) and people with conductive loss (n = 83).

Statistical analyses were conducted using R Version 1.0.44[211] with packages dplyr[212] and lmerTest.[255]

6.4 Results

The current analysis focused on 1274 participants (for flow-chart of participant eligibility and inclusion see Figure 5). Most participants with incomplete hearing and cognitive data participated by questionnaire only and did not come for an examination. Differences in age, sex, PTA, WRCM, and TMT between the eligible at baseline sample and the analytic sample were minor and non-significant (Supplementary Material 3, Table S6.1).

Participants were mostly Caucasian (98%), 51% were women and they had a mean age of 49 (range 30–75) years at baseline (for descriptive statistics see Table 6.1). PTA decreased on average 0.5 dB per year, WRCM 0.7% per year, and TMT 0.05 *SD* per year. The average follow-up time was 9.5 years.

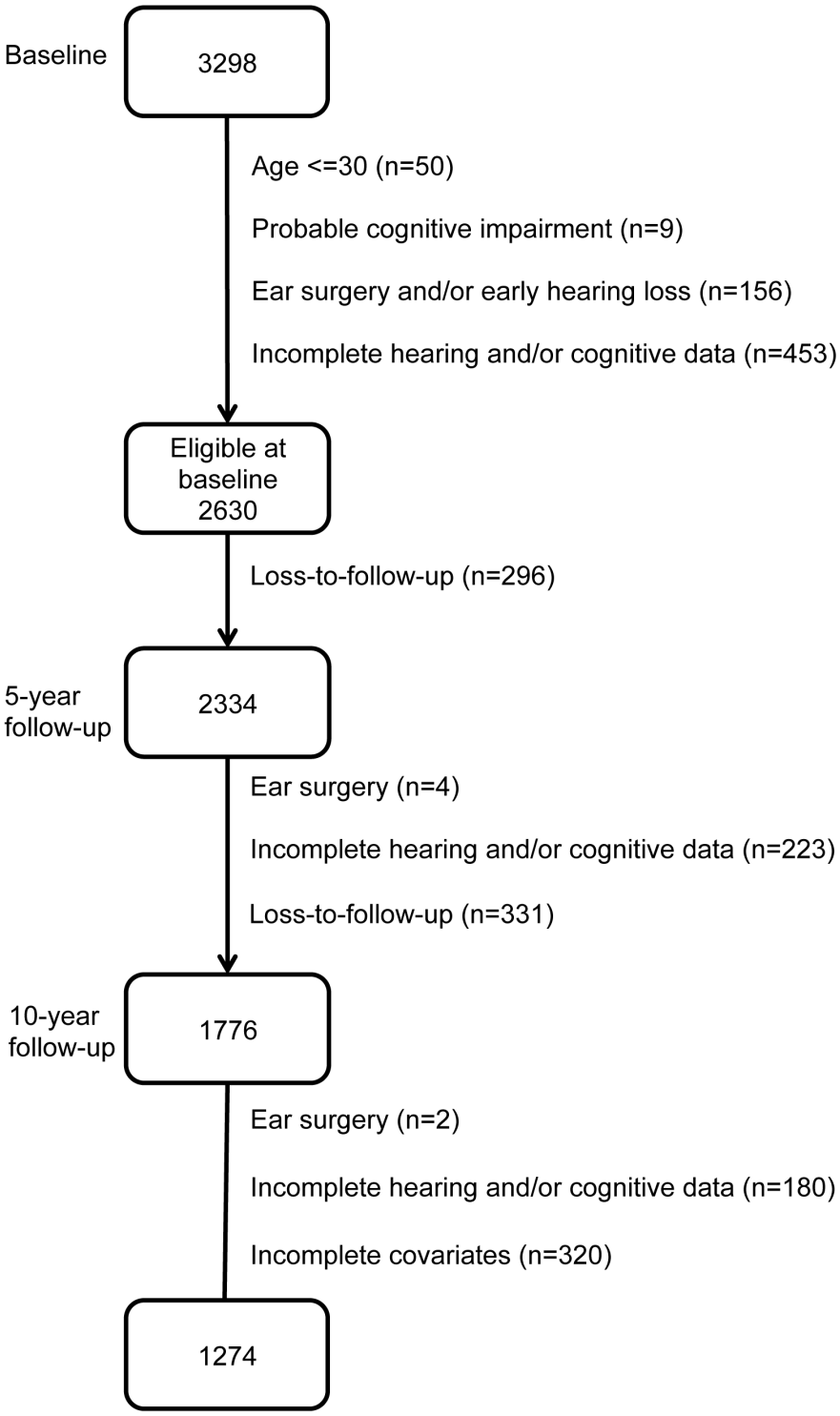

Figure 5. Flow-chart of Participant Eligibility and Inclusion.

Table 6.1. Characteristics of the Analytic Sample (n = 1274) at Baseline Assessment of the Beaver Dam Offspring Study (2005–2008)

Characteristic	
Age, yrs, *M (SD)*	48.7 (8.4)
Women, *n (%)*	656 (51.5)
Education, *n (%)*	
12 years or less	404 (31.7)
13 years or more	870 (68.3)
Hearing	
Loop diuretics intake, *n (%)*	8 (0.6)
Occupational noise exposed, *n (%)*	531 (41.7)
PTA, dB HL, *M* (*SD*)	8.9 (8.5)
WRCM, % correct, *M* (*SD*)	64.5 (13.9)
Cognition	
TMT B, s, *M* (*SD*)	64.1 (25.0)
Comorbidities	
History of cardiovascular disease, *n (%)*	75 (5.9)
Current smokers, *n (%)*	196 (15.4)
Diabetes, *n (%)*	62 (4.9)
Depression, *n (%)*	304 (23.9)

Note. *M*, mean; *SD*, standard deviation; PTA, pure-tone average 0.5-4 kilo Hertz; dB HL, decibel hearing level; WRCM, word recognition with competing message; TMT, Trail-making Test.

6.4.1 Association of PTA and WRCM

Better PTA was associated with better WRCM performance and slower decline in the linear mixed-effects model. WRCM significantly differed by 0.37% per dB difference in PTA (95% CI -0.44,-0.30; standardized ß = -.23) in the age-sex adjusted model. This effect was marginally smaller in the fully adjusted model (-0.36; 95% CI -0.42,-0.29; standardized ß = -.22). WRCM decline significantly accelerated 0.03% per year per dB difference in PTA (95% CI -0.03,-0.02; standardized ß = -.28) in both models.

In the linear regression models, the significant effect of PTA baseline on WRCM at 10-year follow-up (standardized ß = -.30) was almost twice as big as the significant effect of WRCM baseline on PTA at 10-year follow-up (standardized ß = -.18). Effect sizes were not attenuated with adjustment for confounding (Table 6.2).

6.4.2 Association of WRCM and TMT

Better WRCM was associated with better TMT performance and with slower decline in the linear mixed-effects model. TMT performance differed 0.002 *SD* per 1% WRCM performance difference (95% CI -0.004,-0.0002; standardized ß = -.03). The effect was not statistically significant in the fully adjusted model (-0.0015; 95% CI -0.003,0.0003; standardized ß = -.02). TMT performance decline significantly accelerated 0.0003 *SD* per year per 1% WRCM performance difference (95% CI -0.0004,-0.0001; standardized ß = -.14) in both models.

In the linear regression models, the significant effects of WRCM baseline on TMT at 10-year follow-up and TMT baseline on WRCM at 10-year follow-up were equal (standardized ß = -.05). Effect sizes slightly decreased with adjustment for confounding (Table 6.2).

6.4.3 Association of PTA and TMT

Better PTA was associated with better TMT performance and slower decline in the linear mixed-effects model. TMT performance significantly differed 0.008 *SD* per dB difference in PTA (95% CI 0.004,0.013; standardized ß = .08) in the age-sex adjusted model. The

effect size was reduced after adjustment for further confounders (0.005; 95% CI 0.001,0.01; standardized ß = .05). TMT decline significantly accelerated 0.0005 *SD* per year per dB PTA difference (95% CI 0.0002,0.0007; standardized ß = .08). The effect was comparable in the fully adjusted model (0.0005; 95% CI 0.0002,0.0008; standardized ß = .09).

In the linear regression models, the non-significant effects of PTA baseline on TMT at 10-year follow-up and TMT baseline on PTA at 10-year follow-up were comparable but negligible (standardized ß = .02 and .01 respectively). Effect sizes decreased with adjustment for confounding (Table 6.2).

Sensitivity Analyses

Effect sizes remained the same, when we reran analyses excluding participants with conductive hearing loss (n = 83). When we reran analyses excluding hearing aid users (n = 53), effects were slightly weaker in associations between PTA and WRCM and similar in the remaining (Supplementary Material 3, Tables S6.2–S6.5).

Table 6.2. Relation between Each Measure at Baseline (PTA/WRCM/TMT) with Each Other Measure at the 10-year Follow-up

	Change (95% confidence interval) per one unit increase [standardized effect]					
	PTA at 10-year follow-up [dB]		**WRCM at 10-year follow-up [%]**		**TMT at 10-year follow-up [*SD*]**	
	Age-sex adjusted	Fully adjusted	Age-sex adjusted	Fully adjusted	Age-sex adjusted	Fully adjusted
PTA at baseline [dB]			-0.61 [a] (-0.71,-0.52)	-0.61 [a,b] (-0.71,-0.51) [ß=-.30]	0.005 [a] (-0.001,0.011)	0.002 [a,b,c] (-0.004,0.008) [ß=.02]
WRCM at baseline [%]	-0.15 [a] (-0.17,-0.12)	-0.15 [a,b] (-0.17,-0.12) [ß=-.18]			-0.005 [a] (-0.01,-0.002)	-0.004 [a,b,d] (-0.01,-0.001) [ß=-.05]
TMT at baseline [*SD*]	0.17 [a] (-0.22,0.56)	0.13 [a,b,c] (-0.27,0.54) [ß=.01]	-1.20 [a] (-2.03,-0.37)	-0.93 [a,b,d] (-1.78,-0.07) [ß=-.05]		

Note. dB, decibel; PTA, pure-tone average of 0.5-4 kilo Hertz dB hearing level; WRCM, word recognition with competing message; TMT, Trail-making Test performance; *SD*, standard deviation

[a] Result of multivariable linear regression model adjusted for age, sex, and dependent variable at baseline (performance in quartiles).

[b] Further adjusted for income, education, regular exercise, high-sensitivity C-reactive protein levels, interleukin-6 levels, history of cardiovascular disease, smoking, intima-media thickness, occupational noise exposure, and loop diuretics intake.

[c] Further adjusted for years of musical training, body mass index, history of heavy drinking, depression, diabetes, and non-high-density lipoprotein cholesterol levels.

[d] Further adjusted for chemotherapy.

6.5 Discussion

We found weak relationships between two measures of hearing and cognition in middle-aged adults over a 10-year follow-up period. There was no predominant pathway of effects going from hearing to cognitive decline and vice versa. The pathway from hearing to higher-order processing decline was more pronounced in the association of the two hearing tests.

Our results are in line with longitudinal studies of hearing sensitivity, central auditory processing, and cognition[15,24,26,179–181] and extend this research to different aspects of hearing, middle-aged adults, and assessment of temporality of effects. Using two different hearing measures allows us to investigate the complex relationship of auditory and cognitive processing. Decreased hearing sensitivity caused by cochlear defects can be measured by pure-tone audiometry[67] and thus reflects the most sensorineural processing measure. The more complex task of speech understanding in competing message displays central abnormalities[179] and was operationalized as a measure of higher-order auditory processing capabilities. To assess the most upstream higher-order central processing we used the cognitive test. Importantly, in order to understand the development of age-related diseases from early onset onwards, we wanted to extend findings to middle-aged adults as previous research primarily focused on elderly adults with more advanced hearing loss.

The longitudinal relations between the hearing functions were moderate. However, effects between hearing and cognition were small and weakest for hearing sensitivity and cognition. This is consistent with results of a recent meta-analysis (r = -.09) which combined nine longitudinal studies on hearing sensitivity and different cognitive domains.[15] Such small effects might imply that even if there was a causal effect of hearing on cognition, any potential benefit from amplification with hearing aids for restoring or preserving cognitive functions would be limited, and hearing aids do not restore normal hearing.

In order to assess the different possible mechanisms for the longitudinal associations, we compared the extent of effects going both directions – from hearing decline to higher-order central processing decline and vice versa. We found both effects to be present.

6.5.1 Effect of Hearing on Higher-order Processing

Different theories propose a causal effect of hearing loss on cognitive decline. The information degradation hypothesis[183] states that hearing loss increases cognitive load during auditory processing which might negatively affect cognitive functioning. Correspondingly, elderly with hearing impairment recruit wider brain networks during perceptional tasks.[58] According to this hypothesis, effects of hearing on cognition are immediate and potentially remediable. In contrast, the sensory deprivation hypothesis[182] posits that perceptual decline causes permanent cognitive decline. Hearing impairment would alter brain structure which would cause cognitive impairment.[184] Animal studies indicate reorganization within different processing stages and parts of the central auditory system after sensory deprivation.[272] Correspondingly, our results indicate a strong effect of hearing sensitivity on central auditory processing. However, the biological mechanism how a potential reorganization leads to impaired central auditory processing and how it further could cause detrimental brain changes and cognitive decline remains unknown. We found limited support for effects of hearing on cognition in midlife. There were weak effects from central auditory processing to cognition and none from hearing sensitivity to cognition. Consistently, previous studies report stronger effects of central auditory processing than of hearing sensitivity on cognition.[16] Further, associations between hearing sensitivity and cognition appear consistently small in non-impaired populations. Effects are stronger when cohorts are older and/or more hearing impaired.[15] Finally, correspondingly, a recent study found an effect of hearing sensitivity on cognition only in verbal/auditory tests but not non-auditory tests (including TMT)[264] which might reflect the task impurity problem.

6.5.2 Effect of Higher-order Processing on Hearing

According to the cognitive load on perception hypothesis,[182,183] declining cognitive capacity places a cognitive load on perception, which is then poorer. Evidence for this hypothesis is scarce[186] and previous work questions that cognitive decline precedes sensory decline.[264,273] Accordingly, we saw a very small effect from cognition to central auditory processing and the effect from central auditory processing to hearing sensitivity was

only half as big as the opposite effect. Therefore, this mechanism might be present but not the most dominant one.

6.5.3 The Common Cause Effect

Besides both causal pathways being simultaneously present, a common cause might induce decline in both systems. Several sensory functions have been related to cognitive function[178] and concurrent changes in multiple perceptual and cognitive domains suggest a systemic central nervous system pathology and common neurodegenerative etiology. In line with this suggestion, we found that pathways between hearing and cognition and vice versa were of equivalent magnitude. Further, effects from hearing to cognition substantially decreased with adjustment for known confounders. Residual confounding might exist. Promising candidates for a common cause of neurodegeneration may be cardiovascular abnormalities, metabolic dysregulation, and inflammation.[184,274] We might still lack adequate, sensitive measures for these processes.

6.5.4 Limitations

Our middle-aged sample showed little longitudinal change in central auditory and cognitive function, which might contribute to the weak effects between hearing and cognition. The inclusion of complete cases only and loss to follow-up might have further prompted this, given a potentially rather healthy sample. Yet, the eligible baseline sample did not differ to the analytic sample in any relevant baseline characteristic.

We could not replicate the significant small effect of PTA on TMT found in the linear mixed-effects model with less data points in the linear regression model, likely due to reduced power to detect this small effect.

Behavioral measures cannot completely distinguish sensory from central auditory processing. Pure-tone audiometry relies on central processing e.g. regarding the behavioral response. Central auditory processing was tested with an adjusted hearing level. Still, hearing levels impact speech understanding e.g. through distorted signal.[67] This task impurity might have induced an overestimation of effects between hearing tests. Additionally, different sensitivities to detect decline in hearing and cognition might affect the

assessment of temporality of effects. However, we controlled for baseline levels of outcome measures, which limits this potential bias.

Age-related hearing loss and cognitive decline have considerable consequences for quality of life and public health. Better understanding of the mechanism for their co-occurrence in the process of aging has the potential to inform future research directed at prevention and treatment applications. In order to explore a common pathology, a holistic and systematic investigation of neurotoxins, metabolic, vascular, and inflammation processes as well as more sensitive measures, e.g. of microvascular pathology, might advance the field.

In conclusion, decline in hearing sensitivity might affect central auditory processing decline. Central auditory processing had bidirectional relations over time with cognition. Worse baseline hearing measures were associated with cognitive decline and worse baseline cognition was associated with hearing decline. However, these effects were weak in middle-aged adults. We should be cautious in concluding causal effects, as underlying biological mechanisms still remain fairly unclear. Improved hearing might have limited benefit for prevention or delay of cognitive decline.

7 General Discussion and Conclusion

Age-related hearing loss is a disabling condition that has been associated with many other negative health outcomes. Age-related hearing loss prevalence is high and strongly increases with age. Therefore, the burden of hearing loss becomes a major public health concern. The main aims of this thesis were to gain insights into the etiology of and potential treatment strategies for age-related hearing loss. Specifically, the aims were (1) to assess to what extent hearing sensitivity and different cognitive functions influence central auditory processing across the adult life span in the population of the Rhineland Study; (2) to investigate the benefit of motor synchronization on auditory performance and whether previous musical training and cortical thickness of specific brain regions relate to different aspects of the auditory-motor synchronization process in a student pilot population of the Rhineland Study; (3) to assess the temporal relations of hearing sensitivity, central auditory processing, and cognition by using longitudinal data from the Beaver Dam Offspring Study.

In this chapter, I will first present the main findings of this thesis, both in light of existing research and with respect to potential clinical implications. Thereafter, methodological considerations with respect to study designs and validity of the results will be discussed. The focus will be on general considerations because specific limitations have already been discussed in the individual studies and respective chapters. Finally, future perspectives of the field will be outlined.

7.1 Main Findings

7.1.1 Determinants of Central Auditory Processing

We assessed to what extent hearing sensitivity and different cognitive functions influence central auditory processing ability across the adult life span (Chapter 4). We showed that hearing sensitivity is most important for central auditory processing. Furthermore, crystallized intelligence and executive functions showed effects on speech understanding in noise, as opposed to memory functions, which seemed less important.

Thus the ability to perceive speech signals might play a major role in speech understanding in noise, while cognitive functions are supposedly beneficial at a later speech processing stage, with different involvement of different cognitive functions. Better verbal intelligence and lexical knowledge should help in recognizing single words and completing the sentence even if the signal is disrupted through noise. Accurate control of attention and inhibition and better temporal processing also facilitate speech perception (in noise). The working memory capacity of most individuals might be sufficient for the purpose of keeping in mind and recalling single sentences in speech in noise perception. Long-term memory storage is not needed for speech understanding in noise.

Previous studies found an association between hearing sensitivity and central auditory processing. Those studies were small and based on samples with restricted age-ranges.[32,216] We extend previous findings by showing that the association exists over the entire adult life span and across different hearing ability levels. Moreover, studies linking central auditory processing to cognition had heterogeneous samples with different age ranges, levels of hearing sensitivity loss, and had different inclusion criteria regarding hearing aid use.[72] These previous studies did not control for hearing thresholds and/or did not assess different cognitive domains in one model. It is important to assess the relative effect of different cognitive functions to find out underlying mechanisms. When only one cognitive measure is used, this does not only reflect the specific cognitive function that the test is considered to capture but it is also heavily influenced by the general cognitive ability of the person. Our study was able to extend previous results and determine the relative contribution of different cognitive functions for central auditory processing.

This facilitates our understanding of possible functions and mechanisms involved in central auditory processing which might inform future research on possible training methods.

7.1.2 Beneficial Effect of Auditory-motor Synchronization for Hearing Function

We investigated a beneficial effect of motor synchronization on auditory performance with meaningful auditory material in a complex task. We further assessed how previous musical training and cortical thickness of specific brain regions relate to different aspects of auditory-motor synchronization (Chapter 5). Although melody discrimination improved with better tapping synchrony, it was overall worse in the tapping than in the listening only condition. Longer previous musical training and thicker Heschl's gyrus were associated with better melody discrimination and better tapping synchrony. The thickness of the frontopolar cortex could explain who showed and who did not show benefits in the tapping condition. Our results support the simultaneous involvement of two different mechanisms – the alignment of movement with sensory input and the alignment of temporal attention – in the effect of motor synchronization on auditory function.[116] People can benefit from tapping, when they tap accurately enough to align their motor processing with the auditory input. Additionally, they need to align their attention to benefit from this sensory enhancement. According to our findings, Heschl's gyrus might be important for auditory and motor processing and one of the neural correlates of the attentional process might be the frontal pole. However, also other more widespread cortical regions are likely involved in this.

Previous research on enhanced processing through motor synchronization has been limited to easy tasks with simple stimulus material.[113–116] We extended these findings by showing a beneficial effect of sensory-motor synchronization for auditory perception of complex auditory stimuli. Moreover, we determined how prior musical experience and structural brain differences influence the extent to which an individual can benefit from motor synchronization in complex listening.

This could inform future research directed at development of (personalized) training programs to improve hearing ability or counterbalance hearing loss.

7.1.3 Temporal Association of Hearing and Cognition

We investigated the complex interplay of decline in different hearing functions and cognition through determining the longitudinal associations of (1) hearing sensitivity and central auditory processing, (2) central auditory processing and cognition, and (3) hearing sensitivity and cognition, in middle-aged adults (Chapter 6). We found that hearing sensitivity more strongly affected higher-order central auditory processing than higher-order central auditory processing affected hearing sensitivity. The associations between hearing and cognition were bidirectional and weak. This suggests that loss of hearing ability and cognitive decline may share a common cause rather than impairment in one function preceding and triggering impairment in the other.

Previous prospective studies which assessed the association of hearing and cognition[15,16] had limitations in that they (1) included older study participants only, (2) assessed hearing only with audiometry, and (3) neglected temporality of events and comparisons of the strengths of effects going from hearing to cognition and from cognition to hearing. We addressed each of the limitations, and therefore extended the research to different aspects of hearing, middle-aged adults, and the assessment of temporality of effects.

Our findings inform future research directed at prevention and treatment applications. Specifically, we conclude that hearing improvement may have only a limited benefit for prevention or delay of cognitive decline.

7.2 Methodological Considerations

7.2.1 Cross-sectional versus Longitudinal Study Design

Results from cross-sectional studies should be cautiously interpreted with respect to possible causality. Longitudinal studies are more suitable to disclose directionality of effects. Results in Chapter 4 and 6 are based on cross-sectional data from the Rhineland Study and the experimental pilot study of the Rhineland Study. It is difficult to interpret

the directionality of the relation between cortical thickness and performance in results from the pilot study of the Rhineland Study. We can conclude that a thicker cortex is associated with better motor and auditory function, but we cannot determine whether a thicker cortex has led to better motor and auditory functions or whether people who are better in auditory and motor functions get a thicker cortex in particular areas. This also applies to potential causal effects of musical experience. We can infer that individuals with musical training have better motor and auditory performance, but not resolve whether musical experience leads to better motor and auditory performance or individuals with better motor and auditory performance choose to become musicians. This also relates to the directionality of the association between hearing sensitivity, cognitive function, and central auditory processing investigated in the Rhineland Study. We can only conclude with certainty that individuals who were better in hearing sensitivity, executive functions, and crystallized intelligence were also better in speech in noise perception. Because of the limitation of cross-sectional data, we investigated the association of hearing and cognition over time in the longitudinal data from the Beaver Dam Offspring Study. The results from both projects fit well e.g. in that both studies show stronger associations between hearing sensitivity and central auditory processing than between cognitive function and central auditory function. Importantly, we were able to compare the effects of different specific cognitive functions in the Rhineland Study, whereas we could determine longitudinal associations in the Beaver Dam Offspring Study. Combining insights from different study designs can broaden and deepen our understanding of the complex mechanism of human aging.

7.2.2 Internal Validity

Internal validity refers to the extent of which a study is able to establish a link between exposure and outcome based on the design and conduction of the study.[275] In the following, I will discuss the potential effects of bias, measurement errors, sample size, and confounding for the internal validity of the studies included in this thesis.

Bias

Selection bias must always be considered in population-based studies since it can lead to an over and/or underestimation of effects. In both the Rhineland Study and the Beaver Dam Offspring Study, the sample was on average higher educated than the general population and participants had lower age-specific hearing loss rates than the general population they were drawn from (Germany[5] and United States of America[6] respectively). Excluding individuals with ear surgeries and early onset hearing loss (in order to focus on age-related rather than other kinds of hearing loss) in the Beaver Dam Offspring Study sample could be a potential reason for this. In the Rhineland Study project, we restricted the sample to those participants with exact hearing sensitivity thresholds only, and excluded participants who had missing hearing sensitivity thresholds above 60 dB HL. Age-specific hearing loss rates were slightly higher in the Beaver Dam Offspring Study compared to the Rhineland Study. In general, age-specific rates also tend to be higher in the United States of American[6] than in Germany.[5] Genetic and cultural aspects might also play a role in the effects we investigated. We excluded non-native speakers in the Rhineland Study and participants of the pilot sample and the Beaver Dam Offspring Study were mainly native speakers. The fact that responders and non-responders of such studies differ is a known limitation. Study participants typically have a higher socioeconomic status, are healthier, and have a healthier lifestyle.[276,277] This may have led to an underestimation or overestimation of effects. The advantage of the two population studies is that the associations were assessed in a sample that covered the whole adult life span. This was not the case in the experimental pilot study. This study was only conducted in young adults. Because of this young sample, we were able to test whether our experiment works and to assess the underlying mechanisms in a potentially rather healthy and homogeneous sample. This sets a solid understanding of underlying mechanisms for more complicated assessments in the elderly population. However, whether such benefits and the advantages seen with respect to musical training and cortical thickness also exist in elderly cannot yet be determined and need to be verified.

A potential disadvantage of longitudinal studies is selective attrition and a resulting potential bias.[278] Data that is missing completely at random do not affect the validity of results. Furthermore, data that is missing at random, in this case unrelated to both hearing

and cognitive function (and also confounding variables), are not of much concern for the validity of results. On the other hand, missing data that are not at random, are more problematic because this could influence the results. In the Beaver Dam Offspring Study project, 2630 participants were eligible at baseline and data of 3 waves of 1274 participants were analyzed. This was partly caused by incomplete hearing and/or cognitive data and/or incomplete covariate data. The largest number of participants in this subsample decided to participate with questionnaires only and their hearing and cognitive function was not assessed. Furthermore, in 627 cases data were missing due to loss-to-follow-up. Missing due to moving and withdrawing consent should be considered missing at random. A serious problem is the loss-to-follow-up due to health issues, which can lead to a rather healthy sample and induce a systematic bias. As this is a middle-aged cohort, little drop out because of health issues would be expected. We do not know whether people that were lost to follow-up are different from the initial sample. However, the sample of participants who were eligible at baseline did not differ to the analytic sample with regards to age, sex, hearing, and cognitive data. Therefore, we do not expect that this had a major influence on our results.

Measurement Errors

Correct classification of individuals' determinants, confounders, and outcomes is essential to achieve accurate results.[275] Sensitivity and precision of measures play a role in this. Within the Rhineland Study, different sensitivities to performance and change of the different cognitive measures might have affected the results. Some tests might be better suitable to measure an underlying general cognitive factor than others and thus the effects of executive functioning and crystallized intelligence but not of memory functions might be partially attributable to different sensitivities of the measures. Potential different sensitivities to change might have also affected the results of the directionality assessed in the Beaver Dam Offspring Study. However, here the analyses were adjusted for baseline levels, which should have limited this bias.

With regards to precision of our behavioral cognitive and hearing measures, the task impurity problem is of interest since it reflects the overlap between used hearing tests, cognitive tests, and between hearing and cognitive tests. As already explained, there is

a strong overlap between pure-tone audiometry and measures of speech in noise performance. Hence, this might have led to an overestimation of the association between the hearing tests in the Beaver Dam Offspring Study and the effect of hearing sensitivity on central auditory processing in the Rhineland Study. However, the central auditory processing tests were presented above threshold in both studies which should decrease but potentially not eliminate this type of bias. While the cognitive measures chosen from the cognitive battery of the Rhineland Study should in principle measure distinct aspects of cognitive function, some overlap always remains (e.g. all tasks need working memory storage to keep in mind the task and executive control to access memory storage and execute tasks). The task impurity problem is of particular interest with regards to the verbal cognitive measures in the Rhineland Study. The Digit Span Task and Verbal Learning and Memory Test were conducted on the basis of auditory stimulus material. In order to reduce a possible influence of hearing sensitivity loss on the cognitive measures, participants who were hearing aid users wore their hearing aids during cognitive testing. Furthermore, there were few hearing impaired participants in our sample and we adjusted for hearing levels in the model.

Another relevant measurement aspect that limits us in our ability to draw firm conclusions is that we are limited to behavioral measures. Such measures might not be perfectly suited to assess underlying mechanisms. We conclude in the Rhineland Study project that effects of cognitive functions might be beneficial at a later speech processing stage. This conclusion is based on information processing theories.[279] However, since we did not use more specific hearing measures, e.g. otoacoustic emissions to detect changes in the perceptional system ear[280] and/or electrophysiologic measures of central auditory processing,[77,281] this remains on a theoretical level. Given the fact, that the longitudinal results from the Beaver Dam Offspring Study show the same pattern longitudinally, it still appears conclusive. In designing such cohort studies, a selection of measures needs to be made. The usage of well-standardized and easy to conduct measures is often preferred over more specific and complicated assessment methods.

Sample Size and Power

The size of the sample is also critical for the statistical power to detect effects. Both population-based studies were empowered to find the expected effects. However, imputing the missing values in the Beaver Dam Offspring Study could have further improved statistical power. The sample size of the piloting sample may have been too small to find the expected effects in other brain regions and to further assess effects in a whole brain approach.

Confounding

The influence of unmeasured and unadjusted confounders is a major concern in research, since it can lead to an over or underestimation of effects.[275] Confounding might be present in all three projects. In the experimental pilot study, general cognitive ability might be a confounder. People with higher general cognitive ability might be more likely to have more musical training and to benefit from auditory-motor synchronization.

The two hearing functions (hearing sensitivity and central auditory processing) and cognition share many risk factors. Risk factors for cognitive decline and dementia include lower education,[282–285] smoking,[284,286–288] diabetes,[289–292] obesity,[290] and vascular factors.[293–298] Given the overlap of risk factors for hearing loss and cognitive decline, confounding is very likely. Both population study projects addressed multiple potential confounders. However, residual confounding might exist, e.g. unaddressed psychiatric diseases and (micro-) vascular pathologies. In the Beaver Dam Offspring Study confounders at baseline were adjusted for only as there was little change in confounder status over follow-up. However, residual confounding might exist.

7.2.3 External Validity

External validity, also referred to as generalizability, should also be considered in population-based studies. We cannot draw any firm conclusion about the effect in other races, since both study populations mainly consisted of Caucasians. Also, we only looked at German and American populations, which may limit generalizability to populations from other countries. The same holds for non-native speakers, as they were excluded in

the Rhineland Study and participants of the pilot sample and the Beaver Dam Offspring Study were mainly native speakers.

7.3 Future Perspectives

There are 155 million elderly people affected with a disabling hearing loss, reflecting the urgent need to improve treatment and prevention. Although people often consider hearing loss as a natural part of aging, not everybody develops hearing loss through their life and some remain disease free even at old age.[4,29,150] This underlines the potential to maintain hearing through prevention methods.

Research has already gained a lot of insight into age-related hearing loss. However, several aspects of age-related hearing loss still remain rather unclear. These are avenues for future research that will be outlined below.

7.3.1 Understanding Age-related Hearing Loss, particularly Speech Understanding in Noise

The pathological processes involved in age-related hearing loss are not sufficiently understood. Relatively little epidemiological research has been conducted on the differences between high and low frequency hearing loss and the configuration of hearing loss in audiometry. Investigating the different risk factors of high and low frequency hearing loss may help distinguish subtypes of hearing loss and might shed light on underlying processes.

While a number of different assessment methods for central auditory processing exist,[77] only few have been used in large longitudinal studies. Particularly measures of temporal processing hold promise for assessing auditory processing in older adults.[32] The use of a combination of behavioral and physiological methods, also covering aspects of listening effort might facilitate our understanding. Also a stronger emphasis on translational research, bringing together the advantages from research from cell and animal models

with prospective observational studies in human has the potential to identify meaningful mechanism in central auditory processing.

7.3.2 Development of Training Methods

To date, few studies have shown benefits from auditory training methods. The fields of sensory-motor training and cognitive training are still developing. To determine the actual benefit of sensory-motor training or cognitive training methods, well-designed randomized controlled trials will ultimately be needed to exclude confounding through self-selection. Furthermore, it is important to investigate whether positive effects on trained abilities translate to other auditory abilities that better reflect functions needed in daily life interactions. Moreover, these effects should be evaluated in elderly people.

Besides effects of sensory-motor synchronization, future studies could further investigate the effect of lexical training on central auditory processing impairments, as vocabulary skills and semantic knowledge are stable until late in life.[229] However, also a global cognitive training of many facets of cognitive function might facilitate auditory processing and might probably translate to daily life.

It is likely that not everybody might benefit equally from each kind of treatment. For instance, personality or predispositions could influence who improves with training, enjoys training, and finally continues with it. Personalized treatments might facilitate training outcomes. It would be necessary to understand the underlying mechanisms involved in the benefit of interventions for this.

7.3.3 Understanding the Association of Hearing Impairment and Cognitive Decline

The association between hearing and cognition has gained growing interest. In a recent Lancet Commissions publication, it was even stated that the management of hearing loss could prevent or delay dementia and thereby decrease the number of dementia cases worldwide by up to 9%.[299] Such statements are precarious, given the lack of evidence for a causal relationship and an understanding of involved mechanisms. Also effects of hearing on cognition in midlife are small, restricting a potential benefit of hearing management for cognition.

Provided the shared risk factors of hearing loss and cognitive function a shared underlying pathology is likely. Correspondingly, decline in age-specific prevalence of hearing loss[6,20] and dementia[300,301] in more recent generations, particularly in western countries, might reflect that we have already started treating hearing loss and cognitive decline with potentially healthier lifestyles, treatment of cardiovascular diseases, and less exposure to hazardous substances and noise. A holistic and systematic investigation of neurotoxins, metabolic, vascular, and inflammation processes as well as more sensitive measures (e.g. of micro-vascular pathology) might advance the field. Observational studies in humans with back and forth translation with fundamental research could identify specific mechanisms. Additionally, longitudinal studies with a long follow-up time could advance our knowledge.

Finally, the efficacy of hearing aid use as a prevention strategy for cognitive decline should be assessed in randomized controlled trials. Recently, a large randomized controlled trial that aims to investigate the effect of hearing aids on cognitive function and other secondary outcomes in older adults above the age of 70 years was started.[302] Importantly, effects of non-auditory cognitive tests should be investigated to avoid confounding of audibility or listening effort in testing conditions. For such trials, however, it needs to be considered at what age people developed the hearing loss and received the hearing aid. A failure of finding effects in older individuals might not exclude the existence of positive effects of hearing aids in younger individuals. It is likely, that the brain adapts to the disturbed auditory signal in hearing loss. A simple amplification of this disturbed signals at an older age might not lead to a more enriched stimulation. Therefore, hearing aids might not help overcome the decreased stimulation in older adults. Hearing aids might potentially be beneficial if they improve the mindful engagement of individuals with their environment through conversations, as the possibly most stimulating input signal.[1]

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Supplementary Material 1

Table S3.1. Information collected by an interviewer as part of the hearing examinations or collected from participants by means of a self-administered questionnaire

Collected by interviewer
- Bestand ein Knalltrauma oder ein Hörsturz innerhalb der letzten 48 Stunden?[a] *(Ja, Nein)*
- Besteht eine Erkrankung oder akute Schmerzen des Außen-, Mittel- oder Innenohrs (z.B. eine Infektion), aufgrund derer Sie sich nicht in der Lage fühlen, an einem Hörtest teilzunehmen (dieser beinhaltet eine Messung des Trommelfells mittels eines Ohrstöpsels)?[a] *(Ja, Nein)*
- Bestehen Defekte (z.B. Löcher) im Trommelfell oder fehlt ein Trommelfell?[b] *(Ja rechts, Ja links, Ja beidseits, Nein)*
- Haben Sie ein Cochleaimplantat? (Dies ist eine chirurgisch hinter dem Ohr eingesetzte Hörprothese.)[b] *(Ja rechts, Ja links, Ja beidseits, Nein)*
o Falls ja: Wann wurde das (erste) Implantat eingesetzt? *(Alter/ Jahr)*[c]
o Falls ja beidseits: Wann wurde das zweite Implantat eingesetzt? *(Alter/ Jahr)*[c]
- Wurde bei Ihnen Tinnitus diagnostiziert? *(Ja, Nein)*
o Falls ja: Wie laut empfinden Sie das Ohrgeräusch auf einer Skala von 1 für "sehr leise, nur in Stille wahrnehmbar" bis 10 für "sehr laut, auch bei lauten externen Geräuschen noch wahrnehmbar"?
o Falls ja: Wie sehr stört Sie das Ohrgeräusch auf einer Skala von 1 für "überhaupt nicht" bis 10 für "sehr stark"?
- Sind Sie heute so schwer erkältet, dass Sie meinen, dass Ihr Hörvermögen beeinträchtigt ist? *(Ja, Nein)*
- Waren Sie innerhalb der letzten 24 Stunden sehr lauten Geräuschen (darunter fällt auch laute Musik) bzw. Lärm ausgesetzt? *(Ja, Nein)*

Collected by questionnaire

- Wie empfinden Sie Ihr Hörvermögen (ohne Hörgerät) auf einer Skala von 1 für "sehr schlecht" bis 10 für "sehr gut"?
- Fühlen Sie sich durch Ihr Hörvermögen im Alltag eingeschränkt oder beeinträchtigt? *(Überhaupt nicht, etwas, mäßig, sehr)*
- Besitzen Sie ein Hörgerät? *(Ja. Nein)*
    - Falls ja: Seit wann haben Sie das Hörgerät? (Bitte Angabe des ersten Hörgerätes, wenn auf beiden Ohren zu unterschiedlichen Zeiten.) *(Alter/ Jahr)*[c]
    - Falls ja: Nutzen Sie Ihr Hörgerät? *(Ja, Nein)*
    - Falls ja: Wie häufig haben Sie Ihr Hörgerät/ Ihre Hörgeräte im letzten Monat genutzt? *(Nie, selten, manchmal, oft, immer)*
- Hatten Sie jemals einen Knall- oder Explosionsunfall? *(Ja, Nein)*
    - Falls ja: Wann hatten Sie den Knall- oder Explosionsunfall? *(Alter/ Jahr)*[c]
- Hatten Sie jemals einen Hörsturz? *(Ja, Nein)*
    - Falls ja: Wann war der letzte/ aktuellste Hörsturz? *(Alter/ Jahr)*[c]
- Sind oder waren Sie in der Freizeit oder auf der Arbeit Lärm ausgesetzt?[d] *(Ja in der Freizeit, Ja auf der Arbeit, Nein weder in der Freizeit noch auf der Arbeit)*
    - Falls ja auf der Arbeit: Wie viel % der Arbeitszeit sind Sie Lärm ausgesetzt? *(0%, 25%, 50%, 75%, 100%)*
    - Falls ja auf der Arbeit: Wie viel % der Arbeitszeit haben Sie Gehörschutz getragen? *(0%, 25%, 50%, 75%, 100%)*
    - Falls ja in der Freizeit: Wie viel % der Freizeit sind Sie Lärm ausgesetzt? *(0%, 25%, 50%, 75%, 100%)*
    - Falls ja in der Freizeit: Wie viel % der Freizeit haben Sie Gehörschutz getragen? *(0%, 25%, 50%, 75%, 100%)*

Each item allowed for a single answer option only, unless otherwise stated.

[a] Contraindication for all auditory examinations

[b] Exclusion criterion for all auditory examinations

[c] Age of participant at event or year of event

[d] Selection of multiple answer options possible

Supplementary Material 2

Table S4.1. Association of Hearing Sensitivity and Different Cognitive Functions with Central Auditory Processing in the Subsample of Complete Cases (n = 1257)

	Fully adjusted [a]
Variable	Speech Reception Threshold difference [dB], (95% CI; p-value)
PTA [dB HL]	0.04 (0.04,0.05; <.001)
MWT-B [*SD*]	-0.07 (-0.12,-0.01; .02)
TMT B [*SD*]	-0.13 (-0.20,-0.07; <.001)
DS [*SD*]	-0.03 (-0.08,0.02; .19)
VLMT [*SD*]	-0.05 (-0.11,0.01; .08)

Note: dB, decibel; PTA, pure-tone average 0.5–4 kilo Hertz; HL, hearing level, MWT-B, Mehrfachwahl-Wortschatz-Intelligenztest; SD, standard deviation; TMT B, Trail-making Test B; DS, Digit Span Task; VLMT, Verbal Learning and Memory Test

[a] Multivariable linear regression model adjusted for age (mean centered), age^2, sex, income, education, hypertension, history of cardiovascular disease, diabetes, body mass index, total cholesterol by high-density lipoprotein cholesterol ratio, lipid-lowering medication intake, C-reactive protein level, depression, ototoxic medication intake, smoking, tinnitus, and occupational noise exposure.

Table S4.2. Association of Hearing Sensitivity and Different Cognitive Functions with Central Auditory Processing in the Subsample Excluding Hearing Aid Users (n = 1653)

	Fully adjusted [a]
Variable	Speech Reception Threshold difference [dB], (95% CI; p-value)
PTA [dB HL]	0.03 (0.03,0.04; <.001)
MWT-B [*SD*]	-0.10 (-0.15,-0.06; <.001)
TMT B [*SD*]	-0.12 (-0.18,-0.07; <.001)
DS [*SD*]	-0.02 (-0.06,0.02; .35)
VLMT [*SD*]	-0.06 (-0.11,-0.01; .01)

Note: dB, decibel; PTA, pure-tone average 0.5–4 kilo Hertz; HL, hearing level, MWT-B, Mehrfachwahl-Wortschatz-Intelligenztest; SD, standard deviation; TMT B, Trail-making Test B; DS, Digit Span Task; VLMT, Verbal Learning and Memory Test

[a] Multivariable linear regression model adjusted for age (mean centered), age^2, sex, income, education, hypertension, history of cardiovascular disease, diabetes, body mass index, total cholesterol by high-density lipoprotein cholesterol ratio, lipid-lowering medication intake, C-reactive protein level, depression, ototoxic medication intake, smoking, tinnitus, and occupational noise exposure.

Table S4.3. Association of Hearing Sensitivity and Different Cognitive Functions with Central Auditory Processing in the Subsample Excluding Individuals with Impaired Tympanometric Function (n = 1658)

	Fully adjusted [a]
Variable	Speech Reception Threshold difference [dB], (95% CI; p-value)
PTA [dB HL]	0.05 (0.04,0.05; <.001)
MWT-B [*SD*]	-0.10 (-0.15,-0.05; <.001)
TMT B [*SD*]	-0.12 (-0.18,-0.06; <.001)
DS [*SD*]	-0.01 (-0.06,0.03; .58)
VLMT [*SD*]	-0.05 (-0.11,0.00; .05)

Note: dB, decibel; PTA, pure-tone average 0.5–4 kilo Hertz; HL, hearing level, MWT-B, Mehrfachwahl-Wortschatz-Intelligenztest; SD, standard deviation; TMT B, Trail-making Test B; DS, Digit Span Task; VLMT, Verbal Learning and Memory Test

[a] Multivariable linear regression model adjusted for age (mean centered), age^2, sex, income, education, hypertension, history of cardiovascular disease, diabetes, body mass index, total cholesterol by high-density lipoprotein cholesterol ratio, lipid-lowering medication intake, C-reactive protein level, depression, ototoxic medication intake, smoking, tinnitus, and occupational noise exposure.

Supplementary Material 3

Equation 1

Equation of the linear mixed-effects model of hearing sensitivity (PTA) and central auditory processing (WRCM)

$$WRCM_{ij} = ß_0 + ß_1 age_{ij} + ß_2 agegroup_i + ß_3 sex_i + ß_4 PTA_{ij} + ß_5 PTA_{ij} * age_{ij} + ß_6 CV_i + U_{0i} + U_{1i} * age_{ij} + e_{ij}$$

$WRCM_{ij}$ is the word recognition with competing message performance [% correct] of i^{th} participant at j^{th} occasion

age_{ij} is the age (centered with baseline mean) of i^{th} participant at j^{th} occasion

$agegroup_i$ is the age group at baseline in 10 year groups of i^{th} participant

sex_i is the sex of i^{th} participant

PTA_{ij} is pure-tone audiometry performance of i^{th} participant at j^{th} occasion

CV_i is the vector of covariates at baseline of i^{th} participant

U_{0i} is the random intercept

U_{1i} is the random slope

e_{ij} is the residual error

Equation 2

Equation of the linear mixed-effects model of central auditory processing (WRCM) and cognition (TMT)

$$TMT_{ij} = ß_0 + ß_1 age_{ij} + ß_2 agegroup_i + ß_3 sex_i + ß_4 WRCM_{ij} + ß_5 WRCM_{ij} * age_{ij} + ß_6 CV_i + U_{0i} + U_{1i} * age_{ij} + e_{ij}$$

TMT_{ij} is the Trail-making Test performance (z standardized with baseline values) of i^{th} participant at j^{th} occasion

age_{ij} is the age (centered with baseline mean) of i^{th} participant at j^{th} occasion

$agegroup_i$ is the age group at baseline in 10 year groups of i^{th} participant

sex_i is the sex of i^{th} participant

$WRCM_{ij}$ is the word recognition with competing message performance [% correct] of i^{th} participant at j^{th} occasion

CV_i is the vector of covariates at baseline of i^{th} participant

U_{0i} is the random intercept

U_{1i} is the random slope

e_{ij} is the residual error

Equation 3

Equation of the linear mixed-effects model of hearing sensitivity (PTA) and cognition (TMT)

$$TMT_{ij} = ß_0 + ß_1 age_{ij} + ß_2 agegroup_i + ß_3 sex_i + ß_4 PTA_{ij} + ß_5 PTA_{ij} * age_{ij} + ß_6 CV_i + U_{0i} + U_{1i} * age_{ij} + e_{ij}$$

TMT_{ij} is the Trail-making Test performance (z standardized with baseline values) of i^{th} participant at j^{th} occasion

age_{ij} is the age (centered with baseline mean) of i^{th} participant at j^{th} occasion

$agegroup_i$ is the age group at baseline in 10 year groups of i^{th} participant

sex_i is the sex of i^{th} participant

PTA_{ij} is pure-tone audiometry performance of i^{th} participant at j^{th} occasion

CV_i is the vector of covariates at baseline of i^{th} participant

U_{0i} is the random intercept

U_{1i} is the random slope

e_{ij} is the residual error

Table S6.1. Comparison of Baseline Characteristics of Eligible at Baseline Sample (n = 2630) and Analytic Sample (n = 1274) of the Beaver Dam Offspring Study

	Eligible baseline sample (n = 2630)			Analytic sample (n = 1274)			Difference
	Mean	**Median**	***SD***	**Mean**	**Median**	***SD***	***p***
Age, yrs	49.2	48	9.4	48.7	48	8.4	.15[a]
PTA, dB HL	9.1	7.5	9.2	8.9	6.9	8.5	1.0[b]
WRCM, % correct	63.6	64	14.4	64.5	68	13.9	.24[a]
TMT, s	67.4	60	32.1	64.1	59	25.0	.07[b]
	Frequency	**Percent**		**Frequency**	**Percent**		***p***
Sex (women)	1449	55.1		656	51.5		.26[c]

Note: *SD*, standard deviation; PTA, pure-tone average of 0.5-4 kilo Hertz; dB HL, decibel hearing level; WRCM, word recognition with competing message; TMT, Trail-making Test performance.

[a] Comparison based on t-test

[b] Comparison based on sign test

[3] Comparison based on chi-square test

Table S6.2. Associations between Each Measure at Baseline (PTA/WRCM/TMT) with Each Other Measure at the 10-year Follow-up in the Subsample after Excluding Hearing Aid Users (n = 1221)

	Change (95% confidence interval) per one unit increase [standardized effect]		
	PTA at 10-year follow-up [dB]	**WRCM at 10-year follow-up [%]**	**TMT at 10-year follow-up [*SD*]**
	Fully adjusted	Fully adjusted	Fully adjusted
PTA at baseline [dB]		-0.51 (-0.62,-0.39)[a] [ß=-.24]	0.001 (-0.008,0.01)[a,b] [ß=.01]
WRCM at baseline [%]	-0.09 (-0.12,-0.07)[a] [ß=-.12]		-0.003 (-0.01,-0.00001)[a,c] [ß=-.04]
TMT at baseline [*SD*]	0.05 (-0.30,0.41)[a,b] [ß=.01]	-0.81 (-1.66,0.03)[a,c] [ß=-.05]	

Note. dB, decibel; PTA, pure-tone average of 0.5-4 kiloHertz dB hearing level; WRCM, word recognition with competing message; TMT, Trail-making Test performance; *SD*, standard deviation.

[a] Result of multivariable linear regression model adjusted for age, sex, dependent variable at baseline (performance in quartiles), income, education, regular exercise, high-sensitivity C-reactive protein levels, interleukin-6 levels, history of cardiovascular disease, smoking, intima-media thickness, occupational noise exposure, and loop diuretics intake.

[b] Further adjusted for years of musical training, body mass index, history of heavy drinking, depression, diabetes, and non-high-density lipoprotein cholesterol levels.

[c] Further adjusted for chemotherapy.

Table S6.3. Associations between Each Measure at Baseline (PTA/WRCM/TMT) with Each Other Measure at the 10-year Follow-up in the Subsample after Excluding Individuals with Conductive Hearing Loss (n = 1191)

	Change (95% confidence interval) per one unit increase [standardized effect]		
	PTA at 10-year follow-up [dB]	**WRCM at 10-year follow-up [%]**	**TMT at 10-year follow-up [*SD*]**
	Fully adjusted	Fully adjusted	Fully adjusted
PTA at baseline [dB]		-0.61 (-0.71,-0.51)[a] [ß=-.31]	0.002 (-0.004,0.01)[a,b] [ß=.01]
WRCM at baseline [%]	-0.14 (-0.17,-0.11)[a] [ß=-.18]		-0.004 (-0.008,-0.001)[a,c] [ß=-.06]
TMT at baseline [*SD*]	0.15 (-0.27,0.57)[a,b] [ß=.01]	-0.96 (-1.84,-0.08)[a,c] [ß=-.06]	

Note. dB, decibel; PTA, pure-tone average of 0.5-4 kiloHertz dB hearing level; WRCM, word recognition with competing message; TMT, Trail-making Test performance; *SD*, standard deviation.

[a] Result of multivariable linear regression model adjusted for age, sex, dependent variable at baseline (performance in quartiles), income, education, regular exercise, high-sensitivity C-reactive protein levels, interleukin-6 levels, history of cardiovascular disease, smoking, intima-media thickness, occupational noise exposure, and loop diuretics intake.

[b] Further adjusted for years of musical training, body mass index, history of heavy drinking, depression, diabetes, and non-high-density lipoprotein cholesterol levels.

[c] Further adjusted for chemotherapy.

Table S6.4. Longitudinal Associations of PTA, WRCM, TMT over 10-year Follow-up in the Subsample after Excluding Hearing Aid Users (n = 1221)

Change (95% confidence interval) per one unit increase [standardized effect]					
Model 1	**WRCM [%]**	***Model 2***	**TMT [*SD*]**	***Model 3***	**TMT [*SD*]**
PTA [dB]	-0.20 (-0.28,-0.12)[a] [ß=-.12]	**WRCM [%]**	0.002 (-0.003, 0.0003)[a,c] [ß=-.02]	**PTA [dB]**	0.01 (0.003,0.01)[a,b] [ß=.07]
PTA x age [dB/yr]	-0.03 (-0.04,-0.03)[a] [ß=-.30]	**WRCM x age [%/yr]**	-0.0002 (-0.0004,-0.0001)[a,c] [ß=-.13]	**PTA x age [dB/yr]**	0.0004 (0.00003,0.001)[a,b] [ß=.05]

Note. dB, decibel; PTA, pure-tone average of 0.5-4 kilo Hertz dB hearing level; WRCM, word recognition with competing message; TMT, Trail-making Test performance; *SD*, standard deviation.

[a] Result of multivariable linear mixed-effects model with age (mean centered at baseline) as the timescale variable; adjusted for random intercept and random slope, baseline age in decades, sex, income, education, regular exercise, high-sensitivity C-reactive protein levels, interleukin-6 levels, history of cardiovascular disease, smoking, intima-media thickness, occupational noise exposure, and loop diuretics intake.

[b] Further adjusted for years of musical training, body mass index, history of heavy drinking, depression, diabetes, and non-high-density lipoprotein cholesterol levels.

[c] Further adjusted for chemotherapy

Table S6.5. Longitudinal Associations of PTA, WRCM, TMT over 10-year Follow-up in the Subsample after Excluding Individuals with Conductive Hearing Loss (n = 1191)

Change (95% confidence interval) per one unit increase [standardized effect]					
Model 1	**WRCM [%]**	***Model 2***	**TMT [*SD*]**	***Model 3***	**TMT [*SD*]**
PTA [dB]	-0.34 (-0.41,-0.27)[a] [ß=-.21]	**WRCM [%]**	-0.002 (-0.003, 0.0003)[a,c] [ß=-.03]	**PTA [dB]**	0.01 (0.001,0.01)[a,b] [ß=.06]
PTA x age [dB/yr]	-0.03 (-0.03,-0.02)[a] [ß=-.28]	**WRCM x age [%/yr]**	-0.0003 (-0.0004,-0.0001)[a,c] [ß=-.14]	**PTA x age [dB/yr]**	0.0005 (0.0002,0.001)[a,b] [ß=.08]

Note. dB, decibel; PTA, pure-tone average of 0.5-4 kilo Hertz dB hearing level; WRCM, word recognition with competing message; TMT, Trail-making Test performance; *SD*, standard deviation.

[a] Result of multivariable linear mixed-effects model with age (mean centered at baseline) as the timescale variable; adjusted for random intercept and random slope, baseline age in decades, sex, income, education, regular exercise, high-sensitivity C-reactive protein levels, interleukin-6 levels, history of cardiovascular disease, smoking, intima-media thickness, occupational noise exposure, and loop diuretics intake.

[b] Further adjusted for years of musical training, body mass index, history of heavy drinking, depression, diabetes, and non-high-density lipoprotein cholesterol levels.

[c] Further adjusted for chemotherapy.

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(African Proverb)

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