General introduction

GENERAL INTRODUCTION

How would our mental life be like if we had no senses? What if you could not see, hear, touch, taste, smell, or sense the world around you in any other way? You would not be able to learn or to react, as both requires sensory input. Would we be able to think? What could we think about without any knowledge gained from our senses? To have a mental life, to perceive the world, we need sensation.[2]

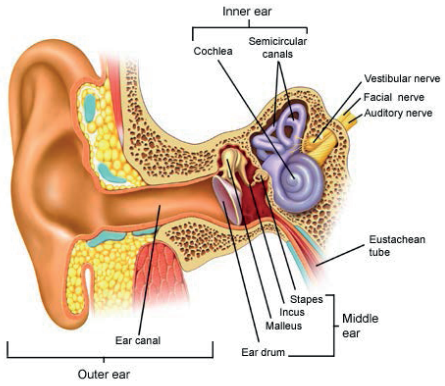

Figure 1. Anatomy of the ear. Source: University of Minnesota Duluth

Our ability to sense is the result of five complex sensory systems: touch, sight, hearing, smell and taste. The organs (skin, eyes, ears, nose, tongue respectively) associated with each sense, sends information to the brain to help us understand and perceive the world around us.[2] Unfortunately, as we grow older, the function of these organs decline. For example, due to degeneration of the olfactory receptor neurons, a high proportion of the elderly population lives with olfactory dysfunction.[3, 4] Another common disorder of the senses with ageing is visual impairment.[5] In addition to these two age-related conditions, hearing loss in the elderly is the most prevalent sensory dysfunction that affects quality of life and daily functioning.

Age-related hearing loss: pathophysiology and prevalence

Age-related hearing loss, also known as presbycusis, is characterized by reduced hearing sensitivity and speech understanding in noisy environments, slowed central processing of acoustic information, and impaired localisation of sound sources.[6] It has primarily been described as a condition caused by damage of the peripheral auditory system (**figure 1**).[6] More specifically, degeneration of the cochlear structures (**figure 1**), including the stria vascularis, the outer hair cells, and the cochlear neurons (**figure 2**), are prominent characteristics of this condition.[7] In terms of symptomatology, age-related hearing loss is characterized by a reduced ability to understand speech, followed by a reduced ability to detect, identify and localise sound sources.[8] Moreover, the abilities to understand speech in noise declines due to diminished central processing, which is also known as central hearing loss.[8] Overall, 10% of the global population has a hearing loss great enough to impair communication, with substantially increasing prevalence with higher age (40% in individuals older than 65 years and 80% in the population above the age of 80).[6, 9] Given the ageing of the population, the oc-

currence of hearing loss is rapidly increasing and the World Health Organization estimated that in 2018, 46 million people in the high income countries had a form of hearing loss, which is expected to increase to 58 million in 2030 and 72 million in 2050 (**figure 3**). With this increasing prevalence, it is inevitable that hearing loss will play an increasingly important role in adult health care. Although direct medical treatment is not possible, hearing aids and cochlear implants are available to partly compensate for the loss of auditory function and possibly delay further degeneration of the auditory system. Besides the use of hearing aids, delaying the onset or slow down the progression of hearing loss in itself may also prove beneficial.

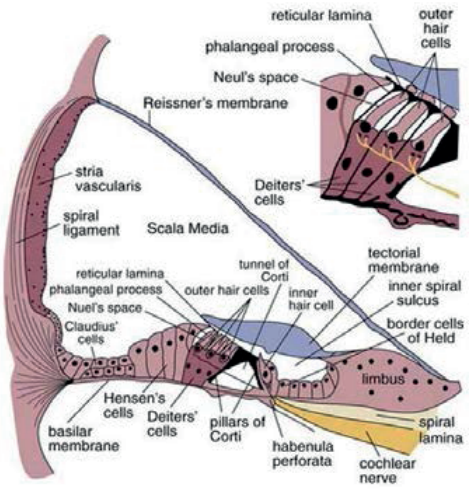

Figure 2. Cochlear anatomy. Source: Clinical Anatomy & Operative Surgery

Risk factors for hearing loss

To be able to delay the onset or slow down the progression of hearing loss, more in-depth knowledge is needed about its risk factors, specifically potentially modifiable ones. Several risk factors for hearing loss have been identified in the past, such as age, educational level, blood pressure, diabetes, smoking and exposure to excessive noise.[10, 11] As such, for example, maintaining a healthy blood pressure, lowering your risk of diabetes by conforming to a healthy lifestyle, and stopping smoking may prevent or delay the onset of hearing loss. Broadening this scientific and clinical knowledge with (longitudinal) population-based studies on risk factors may also support the prevention of potential adverse outcomes associated with hearing loss.

Adverse outcomes of hearing loss

As mentioned earlier, our senses are essential for mental development, so we might expect that a decline in hearing function, and thus a diminished input of auditory signals, will potentially have an impact on mental- and functional brain health. Previous studies have shown that hearing loss is associated with loneliness, social isolation, depression, and an increased risk of falls.[6, 12-14] In addition, recent epidemiological studies reported associations between hearing loss, accelerated cognitive decline and an increased risk of dementia.[15-20] However, the underlying pathway explaining this relationship remains unknown. Does one cause the other, or is a third factor the root cause? A clearer under-

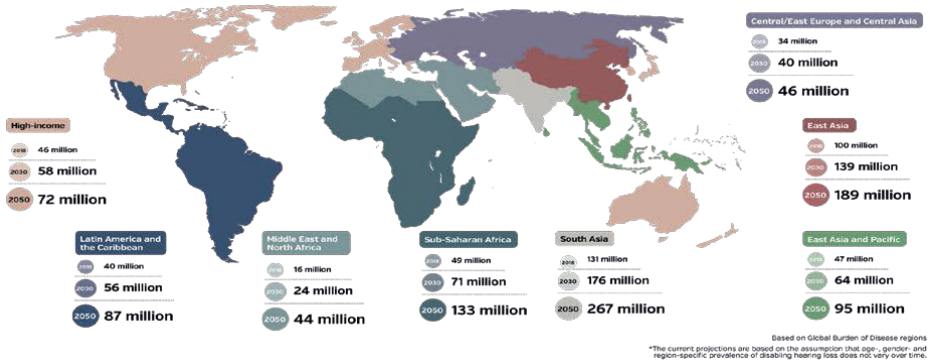

Figure 3. The projected number of people with hearing loss in different world regions until 2050. World Health Organization, Rapport on: WHO global estimates on prevalence of hearing loss. Source: http://who.int/en/news-room.

standing of the nature of the relationship between hearing loss and cognitive decline in the preclinical setting, before full-blown dementia is present, is critical if we are to minimize their impact, either in isolation or together, on quality of life, and to develop effective preventive and rehabilitation strategies. If hearing loss does contribute to accelerated neurodegeneration and cognitive decline, offering hearing aids or other rehabilitative treatments earlier in the course of auditory decline, may prove beneficial in preventing cognitive impairment and possibly even dementia.

Hearing loss and dementia: hypotheses on the potential underlying mechanism

Several hypotheses have been proposed to explain the association between hearing loss and cognitive decline (**figure 4**), of which two will be discussed in this thesis. First, there is the *'Common-Cause Hypothesis'* (**figure 4A**). This view proposes that a common mechanism may underlie both hearing loss and cognitive decline in the elderly and that hearing loss may present itself before the onset of cognitive decline and eventually cognitive impairment, rather than that the two are directly causally related to one another.[21] In regard to this hypothesis, in this thesis, I assess potential risk factors for both hearing function and brain health which are outlined further below. Even though there is support for the common-cause hypothesis, it has been demonstrated that age-related sensory degeneration is also at least in part independent of age-related

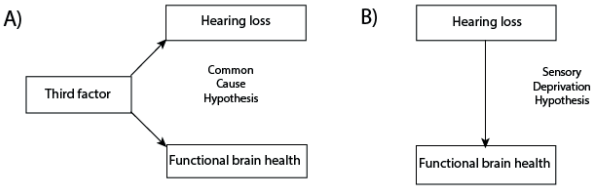

Figure 4. A summary of the hypotheses potentially explaining the relation between hearing loss and cognitive decline.

cognitive degeneration. Such independent contributions would not be observed if a single common-cause was underlying all decline.[22] Following this, there is the second and final hypothesis: the *'Sensory-Deprivation Hypothesis'* (**figure 4B**). This hypothesis poses that declines in perceptual function cause more permanent cognitive declines, possibly through neuroplastic changes that disadvantage general cognition in favour of processes supporting speech perception.[21] The current hypothesis emphasizes that such chronic reallocation of cognitive resources may produce permanent changes in cognitive performance over time. A potential mechanism underlying this hypothesis is thought to be deafferentation and atrophy in the auditory system as well as subsequent reorganization, due to long-term deprivation of sensory input.[21] To explore this hypothesis, I will investigate the interrelation between hearing function, brain health and cognitive function in several studies which are described in more detail below.

Aim of the current thesis

The aim of this thesis is three-fold. I firstly will explore potential risk factors for hearing loss, and secondly, I shall investigate potential risk factors for brain health. The risk factors in this thesis are selected based on current knowledge. To be more specific, cardiovascular disease, body composition, dietary patterns, and vitamin D levels are established risk factors for dementia.[23-26] Analysing these factors in relation to hearing function and brain health may thus add to the current knowledge in regard to the common-cause hypothesis. Thirdly, I will explore interrelations between hearing function and brain health, hopefully contributing to the current knowledge on the sensory-deprivation hypothesis. Important to note: as we do not have (enough) follow-up data yet, I will not be able to elucidate which hypothesis is the 'true' underlying pathway in the association between hearing loss and dementia. Nevertheless, this thesis will add considerably to the current knowledge. For the largest part, my research was embedded within the Rotterdam Study. The Rotterdam Study is an ongoing population-based study, which originated in 1990. It investigates determinants and consequences of ageing.[27] From 2005 onwards, magnetic resonance imaging (MRI) scanning of the brain on a 1.5 tesla MRI scanner was included in the study protocol.[28] Hearing assessment by means of pure-tone audiometry (as a measure of peripheral hearing loss), bone conduction, and a Digits in Noise test (as a measure of central hearing loss) was added to the core study protocol in 2011.[27]

In the following parts of this thesis I discuss various risk factors for hearing function and brain health and the interrelations of both. In **Chapter 2**, I focus on risk factors for hearing loss. **Chapter 2.1** describes the association between body composition (divided into body mass, fat mass, and fat-free mass), diet quality and hearing function. **Chapter 2.2** is dedicated to the association between carotid atherosclerosis, as a marker of generalized cardiovascular health, and hearing function. In **Chapter 3**, potential risk factors for brain health are highlighted. In **Chapter 3.1**, I focus on the relation between diet

quality and brain tissue volumes. Unique in this study is that I use a novel diet quality score. Next, **Chapter 3.2** describes the association between vitamin D status in the Rotterdam population and several markers of brain health, namely: brain tissue volume (total, grey matter, white matter, and the hippocampus), global white matter microstructure (fractional anisotropy and mean diffusivity), white matter hyperintensity volume and the presence and progression of lacunes and microbleeds. The final part of Chapter 3, **Chapter 3.3**, adresses the cross-sectional as well as the longitudinal association between body composition and comparable markers of brain health. In line with Chapter 2.1, I use measures of body mass, fat mass and fat-free mass. **Chapter 4** is dedicated to the interrelations between hearing function and brain health. As hearing loss has been found to be one of the biggest risk factors for tinnitus in the elderly,[29] **Chapter 4.1** focusses on the association between tinnitus and brain tissue volumes. **Chapter 4.2** is embedded within the Atherosclerosis Risk in Community Study, a population-based multisite study in the United States of America. Here, I discuss the association between hearing loss and microstructural integrity of the brain lobes (frontal, temporal, parietal, occipital), the medial temporal lobe structures (hippocampus and amygdala), and the white matter tracts in the brain. **Chapter 4.3** is dedicated to the longitudinal association between hearing loss and cognitive decline. Finally, in **Chapter 5**, I conclude with a review of my main findings in the context of the current knowledge and I will elaborate on future research in hearing function and brain health.

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