

REVIEW ARTICLE

Age-related hearing loss and dementia: whether restoring auditory function can prevent or improve dementia?

Masatoshi TAKEDA, Kunihiro Umayahara, Yukito Ueda, Hidetsugu Wada, Kayo Matsuo, Yoshimi Tsukamoto

Osaka Kawasaki Rehabilitation University

Correspondence: Masatoshi Takeda MD, PhD, President Office, Osaka Kawasaki Rehabilitation University, 158 Mizuma, Kaizuka, Osaka 597-0104, Japan. E-mail: masatakeda@kawasakigakuen.ac.jp

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Abstract

Hearing loss, visual impairment, and memory loss are age-related changes observed in many elderly people. In recent years, hearing loss has become known to be a risk factor for dementia, and the relationship between hearing impairment and dementia has gained increased attention. Age-related hearing loss can be caused by central or peripheral pathology, and degenerative changes of neurites similar to those in the brain of Alzheimer's disease have been observed. The underlying mechanisms of age-related hearing loss includes: similar neurofibrillary degeneration in the cochlea and in the brain; a lack of auditory information from the outside world reducing the input needed to activate brain function; an overload of neural circuits for language processing due to hearing loss, resulting in a lack of cognitive resources; and the mechanism of cognitive deficits in the hippocampus and other areas of information processing is also considered due to less cognitive reserve. While it would be useful to clarify the relationship between hearing restoration and cognitive function through hearing aids and cochlear implants in order to elucidate these mechanisms, further studies are needed on the possibility of hearing restoration and prevention/restoration of cognitive function.

Key words: age-related hearing loss, Alzheimer's disease, cochlear implant, dementia, hearing aid

INTRODUCTION

Hearing difficulty, vision impairment and forgetfulness often gradually become noticeable in old age. These are physiological aging phenomena and are not regarded to be pathological to a certain degree. Age-related hearing loss (ARHL), also called presbycusis, occurs in one-third of people aged 65 years and older (Agrawal, 2008). The World Health Organization defines ARHL as hearing loss of ≥ 26 dB in both ears and categorizes it as slight (26-40 dB), moderate (41-60 dB), severe (61-80 dB), or profound (≥ 81 dB) (Olusanya, 2019). Risk factors of ARHL have been identified as noise exposure, smoking, certain medications, hypertension, and family history (Lin, 2011a). The pathogenesis of ARHL is age-related and characterized by a noticeable loss of auditory sensitivity in the high-frequency range, impaired speech comprehension in noisy environments, reduced auditory information processing speed, and reduced ability to identify the location of the sources of sound (Tavanai, 2017). Severe ARHL has been reported to reduce social connectedness, inducing depression and lower self-esteem (Allen, 2003; Hughes, 2018).

Central auditory dysfunction is presented over time, although in the early stages it predominantly presents as peripheral hearing impairment (Gates, 2005).

ARHL is caused by degeneration of the cochlear hair auditory cells. An increase in reactive oxidants in the mitochondria of inner-ear hair cells leads to mitochondrial DNA (mtDNA) mutations when their accumulation exceeds a certain threshold (Yamasoba, 2013). In the cochleae of elderly people, approximately 32% have a 4977 bp mtDNA defect (Markaryan, 2009). In the inner ears of rats, a 4834 bp mtDNA defect that increases sensitivity to aminoglycoside antibiotics has been reported in over 90% of cases (Kong, 2006). Molecules such as vascular endothelial growth factor (VEGF) (Picciotti, 2006), sirtuin 1/proliferator-activated receptor-gamma coactivator 1 α (SIRT1-PGC1 α) (Xue, 2016), LKB1 (CaMKK/3), and AMPK (Won, 2010) are known to be involved in the degeneration of hairy auditory cells, and these molecules are also involved in the pathology of Alzheimer's disease (Kalaria, 1998). The pathological process of ARHL and Alzheimer's disease thus has some overlap.

AGE-RELATED HEARING LOSS INCREASES RISK OF DEMENTIA

Dementia is defined as impaired ability to remember, think, or make decisions that interferes with doing everyday activities (CDC, 2019), meaning a condition in which social life becomes difficult due to cognitive decline, particularly memory impairment. The prevalence of dementia increases in an equiproportionate manner with age 65 and older, implying the close relationship to brain aging. Cognitive function refers to the ability to select and judge the appropriate response to information from the outside world by comparing it with internal memory. Cognitive function is carried out by the perceptual association cortex, the motor association cortex, and the limbic system (Figure 1). There are various subcategories of cognitive function, and the diagnostic and statistical manual of mental disorders version five (DSM-5) classifies cognitive function into six domains: (complex) attention, executive function, memory and learning,

language, perceptual-motor function, and social cognition (Sachdev, 2014).

Cognitive function is influenced by perceptual information from the outside world and is particularly associated with hearing and visual impairment (Wong, 2010). Dementia has increased incidence in people with hearing impairment (Figure 2), and people with hearing loss are more likely to experience social alienation and isolation (Kay, 1964). Hearing impairment has been shown to be associated with cognitive decline (Lin, 2011b, 2013). A meta-analysis reported that hearing loss in middle age can explain 9% of the factors contributing to the development of dementia (Loughrey, 2018), and the relationship between hearing loss and dementia has gained increased attention. ARHL includes not only damage to peripheral auditory organs but also central damage, implying the possibility that improving hearing may improve or prevent dementia (Jiang, 2023).

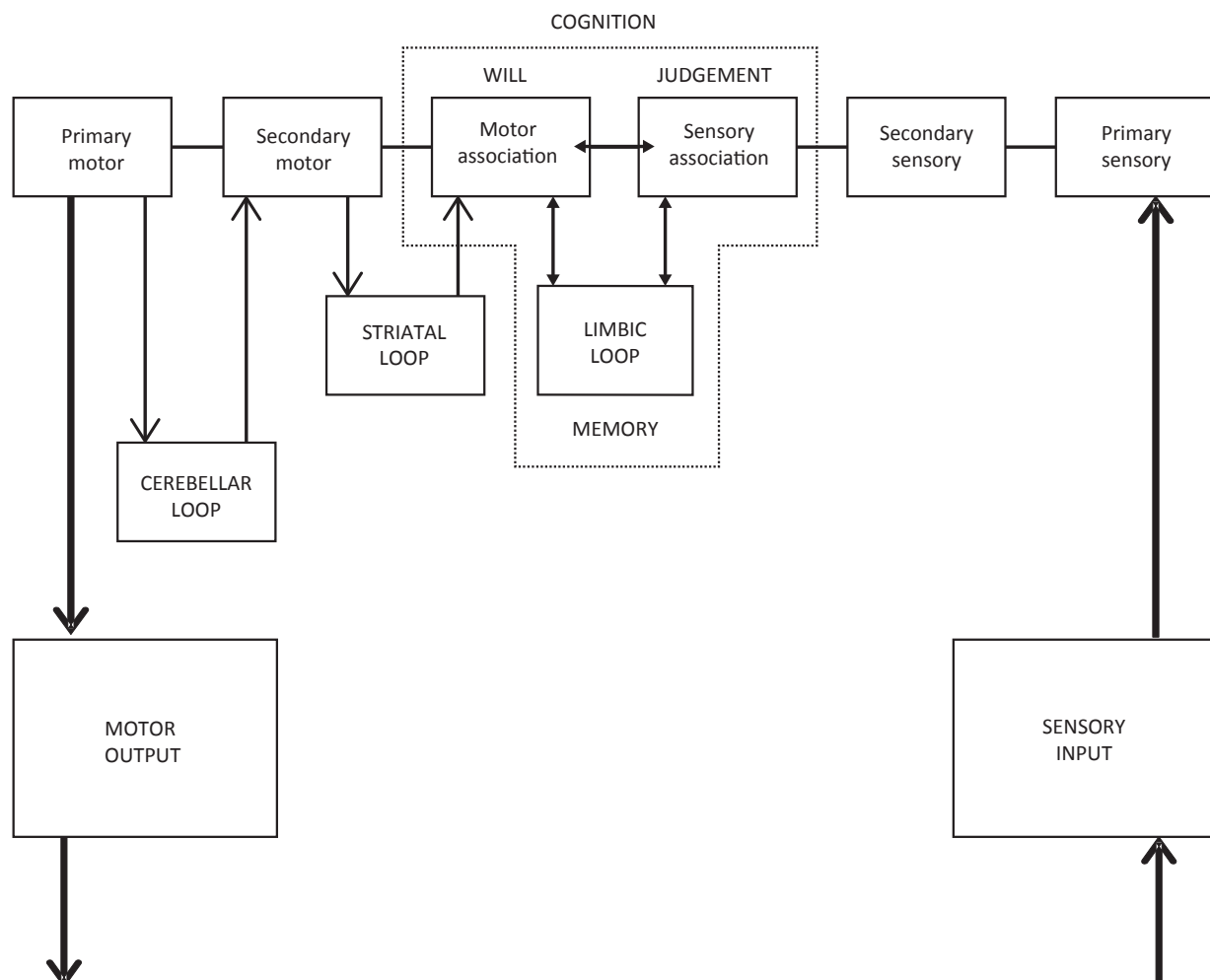


Figure 1. Brain regions responsible for cognitive functions (narrow sense)

In dementia, cerebral functions are not uniformly impaired, rather, there is impairment of sensory association areas, motor association areas, and/or the limbic system. Primary and secondary sensory and motor cortices are basically retained.

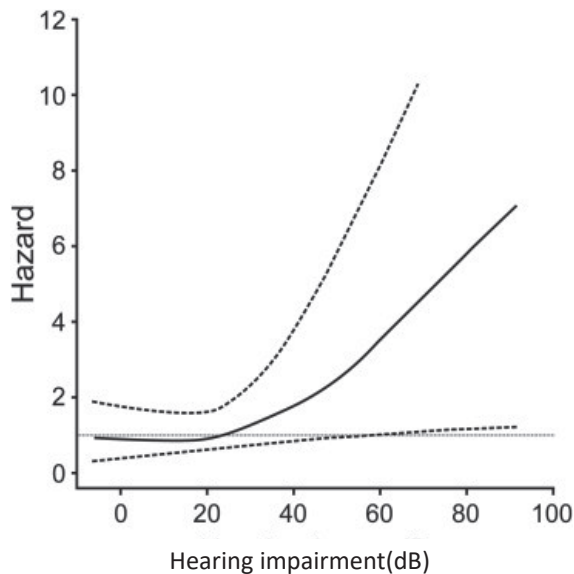


Figure 2. Hearing impairment and cognitive impairment incidence of dementia increases with degree of impairment for hearing loss >25 dB (Adapted from: Lin, FR, Metter, EJ., et al. Hearing loss and incident dementia. *Arch Neurol* 68, 214-220, 2011).

UNDERLYING MECHANISM OF DEMENTIA CAUSED BY ARHL

The relationship between ARHL and cognitive decline is complex and multifactorial, including molecular, neural circuit, and psychosocial levels. Griffiths (2020) asserted the four hypotheses below to explain the relationship between ARHL and dementia.

Hypothesis 1: Pathological processes of neuronal degeneration common to the cochlea and cortex.

ARHL is caused by degeneration of auditory neurons within the cochlea. Meanwhile, degeneration of cortical neurons is the basic pathology of Alzheimer's disease. It is thus possible that there are pathological processes common to both Alzheimer's disease and hearing loss. The neuropathology that characterizes Alzheimer's disease includes senile plaque amyloid and neurofibrillary tangles. Similar to those in neurofibrillary tangles, the ascending auditory nerve nucleus and auditory cortex neurons (Parvizi, 2001) show neurofibrillary degeneration resulting in hearing loss. The VEGF, SIRT1-PGC1 α , and LKB1 (CaMKK β)-AMPK systems are considered common pathologies in Alzheimer's disease and ARHL, and these molecular-level pathologies have been implicated in Alzheimer's disease (Kalaria, 1998; Kumar, 2013; Won, 2010), as well as in the degeneration of cochlear hair cells (Hill, 2016; Picciotti, 2006; Xue, 2016).

However, while cortical neuronal degeneration in

Alzheimer's disease is assumed to be caused by amyloid accumulation (which induces hyperphosphorylation of tau protein and degeneration of neurites), the absence of amyloid deposition in neurons of the auditory system suggests that neurofibrillary-like changes in auditory neurons may represent a neurodegenerative process and not necessarily a common pathological process. Neurofibrillary-like changes in auditory neurons could therefore represent a neurodegenerative process and do not necessarily indicate a common pathological process. Transgenic animal models of Alzheimer's disease have shown degeneration of cochlear neurons, which differs from brain lesions that cause cognitive decline because this neuronal degeneration can be seen at a young age. Vascular lesions may act as a common pathology in both dementia and hearing loss. Vascular pathology of the cochlea is a factor that contributes to ARHL (Kurata, 2016), and vascular lesions have also been found in the ascending nerve and the auditory cortex, which could be a pathology in common with that of vascular dementia.

Hypothesis 2: Insufficient environmental stimulation decreases cognitive reserve.

Some people show no cognitive decline despite the appearance of amyloid deposition and neurofibrillary changes in the brain. The ability to maintain cognitive function by antagonizing the pathology of brain aging and Alzheimer's disease has been postulated and called 'cognitive reserve' (Stern, 2012; Takeda, 2020). The biological nature of cognitive reserve has not been fully elucidated, but there is some acceptance of the idea that the diversity and plasticity of overlapping brain circuits is its main body (Stern, 2020; Takeda, 2022). From this standpoint, it is conceivable that a decrease in auditory input may lead to inadequate stimulation necessary to maintain cognitive function. This could result in a decrease in cognitive reserve and thus an increased susceptibility to developing dementia. Furthermore, a sustained decrease in auditory input may also lead to a decrease in environmental stimuli such as language and conversation, which may negatively affect brain function. Enriched environments have been shown in animal studies to positively affect the maintenance of brain function; rodents in enriched environments were shown to have increased neurogenesis in the hippocampus (Kempermann, 1998; van Praag, 1999). Input from an enriched environment is necessary for the maintenance of brain function, and such environmental input is thought to

be required for cognitive reserve (Song, 2022; Stern, 2012).

The poor input of speech stimuli in people with hearing impairment can make it difficult for them to access verbal and emotional information from speech. Lack of verbal and emotional input may have a negative impact on brain function, which is compounded by the possibility of reduced social interaction due to poor language function, resulting in the emergence of negative effects on cognitive function. Social interactions in old age are often associated with a decline in cognitive function, and reduced social interaction in old age can be a risk for developing dementia (Kuiper, 2015). Moreover, access to language information in noise can be a major challenge for people with hearing loss (Gatehouse, 2004), and difficulties in language comprehension can lead to social withdrawal (Hughes, 2018).

Examinations of the relationship between hearing loss and dementia have largely focused on pure tone hearing loss, but there have been recent suggestions that the relationship between language understanding and dementia is more important than pure tone hearing because language understanding in a noisy environment requires more than pure tone perception (Haggstrom, 2020; Jalaei, 2019). Hearing loss reduces the volume of the medial temporal lobe, but it has also been reported that people in occupations such as musicians and piano tuners tend to maintain brain function and have less reduction in hippocampal volume if they have hearing loss (Herdener, 2010; Hyde, 2009; Teki, 2012). These reports suggest that hearing impairment in middle age may promote atrophy of the hippocampus and parahippocampal gyrus in old age, and that the onset of dementia may be due to reduced cognitive reserve.

Hypothesis 3: Excessive cognitive resources are required for language comprehension.

People with hearing impairment require a comparatively large amount of their cognitive resources for listening comprehension, which may make cognitive resources unavailable for other cognitive functions. Hearing impairment is thus thought to result in a lack of cognitive resources used for attention, working memory, and language processing.

There is perhaps conflict between Hypothesis 2, which seeks the cause of inadequate stimulation of auditory circuits, and Hypothesis 3, which describes the requirement of more cognitive resources for auditory neural circuits compared with other cognitive areas. Conversely, these two hypotheses are not nec-

essarily in conflict if we understand Hypothesis 2 to explain the risk of dementia and Hypothesis 3 to explain the process of cognitive decline after the onset of dementia. The competition for cognitive resources between the auditory system and other cognitive functions is shown as a decrease in performance in dual tasks (tactile perception, visual working memory, Stroop test, etc.) (Haid, 2019; He, 2022), which require listening to a conversation and performing other tasks at the same time. Such a decrease in performance in dual tasks is likely to become apparent in noisy environments or in masked conversations. Performance of a cognitive task is thought to be reduced when attention is focused on a listening task, although no studies have yet examined the delayed replay memory task itself. Functional brain imaging studies have shown that the left inferior frontal lobe and the hippocampus, in addition to the auditory cortex, are active in language comprehension under difficult conditions (Kudela, 2018), suggesting a competition between these regions for cognitive resources. However, the sharing of cognitive resources required for listening in difficult situations is perhaps a temporary phenomenon, and future studies will seek to determine the mechanisms that induce the persistent changes in brain function that lead to dementia.

Hypothesis 4: Brain activity involved in auditory perception and the development of dementia.

A more refined version of Hypothesis 3 focuses on pathology in the medial temporal lobe, which is common to both auditory and cognitive functions. Neurofibrillary tangles, the basic pathology of Alzheimer's disease, are hyperphosphorylated tau lesions that first appear in the medial temporal lobe, centered in the entorhinal cortex and the hippocampus. This region likely plays an important role in auditory information processing. Conditioning experiments with sound stimuli in animals require transient storage of sound information, and the hippocampus is now known to play an important role in this system (Ahmed, 2020). Recently, the array of neurons in the hippocampus has been suggested to be involved in the identification of sounds (Aronov, 2017), and in humans, there is demonstrated involvement of the medial temporal lobe in the analysis of sound patterns (Kalm, 2013). Just as place cells and grid cells in the hippocampus play an important function in the processing and analysis of visual information, there is an assumed involvement of the paralimbic cortex and the hippocampus in the analysis and processing of sound sequences. The function of picking up

and processing speech from noise is thought to be similar to the function of identifying objects from the background in visual space. Considering that such information processing occurs in the medial temporal lobe, neurofibrillary changes in the medial temporal lobe in early Alzheimer's disease may interfere with the auditory information processing function necessary for language comprehension. This may be the case in the early stages of Alzheimer's disease.

In light of the above findings, we can consider a cascade in which the reduction of auditory signals due to hearing loss leads to hyperactivity of neural activity in the medial temporal lobe, which in turn promotes tau deposition and induces hyperactivity of NMDA receptors and excitotoxicity of neurons.

Each of these four hypotheses are in the early stages, and further studies will seek to determine which of them, if any, is correct. However, the results of studies examining the effects of hearing aids and cochlear implants on cognitive function may provide a means of predicting a causal relationship between them.

CAN HEARING AIDS AND COCHLEAR IMPLANTS PREVENT OR IMPROVE DEMENTIA?

Clinical observations of hearing restoration and cognitive improvement have been inconsistent. While some reports suggest that improved hearing helps improve dementia (Acar, 2011; Amieva, 2015; Choi, 2011; Dawes, 2015a,b), others report no such effect (Valentijn, 2005; van Hooren, 2005). Hearing improvement through use of hearing aids was said to not reduce the risk of dementia (Lin, 2011c), while elsewhere hearing aids were said to improve cognitive function (Dawes, 2015a). In evaluating these reports, it may be necessary to distinguish the impact of hearing restoration on cognitive function from the risk of developing dementia and the impact on cognitive decline after the onset of dementia. Reports on the improvement of cognitive function with the use of hearing aids are mixed, and it is not currently possible to determine whether or not there is an effect. Hearing aid use has been suggested to slow the rate of cognitive decline (Maharani, 2018; Amieva, 2015; Deal, 2015; Dawes, 2015a), while other studies report or suggest no such effect (Lin, 2023; Valentijn, 2005). Proper use of hearing aids is well known to require a certain period of habituation and many people discontinue using hearing aids. Certain innovations are often necessary to ensure that patients with dementia continue to appropriately use hearing aids (Claes,

2018).

A systematic meta-analysis of the effects of cochlear implants on cognitive function summarized the results of six papers on hearing correction with cochlear implants in 166 patients and improvement in cognitive function 1-3.7 years after surgery (Claes, 2018). Five of the studies showed improvement in cognitive function, while cognitive function was unchanged in one of the studies. In a report by Ambert-Dahan (2017) in which patients with severe sensorineural hearing loss (23-83 years old) underwent cochlear implantation followed by auditory rehabilitation and verbal cognitive phase training. One year later, cognitive function was assessed by the cognitive disorders examination (CODEX) and the Montreal cognitive assessment (MoCA). Normal cognitive function was restored in four of the eight patients with preoperative cognitive decline, while three of the ten patients without cognitive decline developed cognitive decline (Ambert-Dahan, 2017). In an examination of the effects of hearing aids and cochlear implants in elderly patients with various degrees of hearing loss (Castiglione, 2016), patients with cochlear implant (15 patients) had significantly improved cognitive function by MoCA at 1 year, 27.20 (± 3.72) compared with 25.70 (± 3.08) before surgery ($p < 0.01$). In a study of elderly women (7 patients) 2-4 years after cochlear implant surgery (Cosetti, 2012), cognitive function was significantly improved using the Wechsler Adult Intelligence Scale, Trail Making Test, Boston Call Test, Repeatable Battery for the Assessment of Neuropsychological Status, and there was improvement in cognitive function.

CONCLUSION

We outlined four hypotheses regarding dementia and age-related hearing loss. Further study is needed to determine the correct hypothesis, but the relationship between tension repair and nystagmus is summarized for each of the four hypotheses (Table 1). If Hypothesis 2 or Hypothesis 4 are correct, hearing restoration would likely decrease the risk of dementia but not improve the symptoms. Hypothesis 3 might predict both risk of dementia and improvement in cognitive function. Although the recently reported effect of use of hearing aids in the prevention of dementia has not been clearly demonstrated, it is hoped that the results of future clinical studies will clarify the relationship between hearing impairment and the development of dementia.

Table 1. Can hearing restoration improve risk and progression of dementia?

		Risk change by hearing improvement	Cognitive improvement by hearing improvement
Hypothesis 1	Common pathology	no change	no
Hypothesis 2	Decreased input	decreased risk	no
Hypothesis 3	Insufficient cognitive resource	no risk	yes
Hypothesis 4	Common MTL pathogenesis	decreased risk	no

Although we cannot yet determine which of the four hypotheses is correct, Hypothesis 4 is the most likely at this time. Hypothesis 4 states that use of hearing aids or cochlear implants to restore hearing reduces the risk of dementia, but it is unlikely to prevent cognitive decline after the onset of the disease. (adopted from Griffiths et al.)

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