Review

Understanding the Relationship Between Age-Related Hearing Loss and Alzheimer's Disease: A Narrative Review

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Abstract. Evidence suggests that hearing loss (HL), even at mild levels, increases the long-term risk of cognitive decline and incident dementia. Hearing loss is one of the modifiable risk factors for dementia, with approximately 4 million of the 50 million cases of dementia worldwide possibly attributed to untreated HL. This paper describes four possible mechanisms that have been suggested for the relationship between age-related hearing loss (ARHL) and Alzheimer's disease (AD), which is the most common form of dementia. The first mechanism suggests mitochondrial dysfunction and altered signal pathways due to aging as a possible link between ARHL and AD. The second mechanism proposes that sensory degradation in hearing impaired people could explain the relationship between ARHL and AD. The occupation of cognitive resource (third) mechanism indicates that the association between ARHL and AD is a result of increased cognitive processing that is required to compensate for the degraded sensory input. The fourth mechanism is an expansion of the third mechanism, i.e., the function and structure interaction involves both cognitive resource occupation (neural activity) and AD pathology as the link between ARHL and AD. Exploring the specific mechanisms that provide the link between ARHL and AD has the potential to lead to innovative ideas for the diagnosis, prevention, and/or treatment of AD. This paper also provides insight into the current evidence for the use of hearing treatments as a possible treatment/prevention for AD, and if auditory assessments could provide an avenue for early detection of cognitive impairment associated with AD.

Keywords: Age-related hearing loss, Alzheimer's disease, cognitive function, hearing loss

INTRODUCTION

With a rapidly aging population, the prevalence of dementia has increased and is proposed to continue to increase [1]. Currently, it is estimated that 57 million people worldwide are diagnosed with demen-

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tia [2]. The number of dementia cases worldwide is expected to double every 20 years if there is no medical breakthrough, resulting in an estimated 152 million cases by 2050 [1, 2]. Hearing loss is suggested to be one of the modifiable risk factors for dementia contributing to the population attributable fraction of dementia cases worldwide. Hearing loss is estimated to account for 8% of dementia cases, that is, approximately 4 million of the 50 million cases of dementia worldwide may be attributed to untreated hearing loss [3]. Evidence indicates that hearing loss, even at mild levels, increases the long-term risk of cognitive decline and incident dementia [3–6]. Understanding the relationship between hearing loss and dementia has attracted greater public health attention. Increasing this understanding can provide valuable insights for the development of early detection tools and effective treatment interventions.

DEMENTIA AND ALZHEIMER'S DISEASE

The majority of dementia cases are due to Alzheimer's disease (AD) neuropathology, which accounts for 60–80% of all dementia cases [7] and is defined by loss of episodic memory and impaired cognitive function combined with the presence of biomarkers of AD [8]. Neurodegenerative changes, which lead to AD, are suggested to start to accumulate 10 to 20 years before the appearance of clinical symptoms (see Fig. 1) [9, 10]. In addition to neuronal and synaptic loss, AD is defined by other neuropathological features, namely, extracellular amyloid-β (Aβ) deposition found in senile plaques, and hyperphosphorylated tau protein which causes the formation of neurofibrillary tangles in neural cell bodies [11–13]. Aβ is a product of the amyloid-β protein precursor (AβPP) after the sequential cleavage by the enzymes β-secretase and γ-secretase. Improper folding of the cleaved AβPP by β-secretase is suggested to result in overproduction of misfolded proteins, which in turn accumulate into senile plaques [14, 15]. Aβ build-up is closely linked to synaptic and neuronal damage, which in turn result in gradual neuronal death and the deterioration of cortical and subcortical structures, i.e., brain atrophy [11].

AD neuropathology also features abnormal concentrations of total and phosphorylated tau protein in the brain that can be accurately reflected in the cerebrospinal fluid (Fig. 1) When tau protein is hyperphosphorylated, microtubules in the cytoskeleton of neurons begin to break down and this causes the development of insoluble neurofibrillary tangles inside the neural cell bodies [12, 15]. It is suggested that the formation of these tangles progresses from brain structures such as the transentorhinal cortex to structures such as the hippocampus and the neocortex [16]. The appearance of tau pathology in the neocortex coincides with cognitive impairment [17]. These neurodegenerative changes are characterized by synaptic loss, neural damage, imbalances in neurotransmitters, and finally, manifest into the clinical cognitive symptoms of AD [11, 18].

The National Institute on Aging-Alzheimer's Association (NIA-AA) group has suggested a concept that subdivides the course of AD into three subsequent stages. The first stage, known as the preclinical stage of AD, is characterized by having no impairment in cognition based on standard cognitive assessments and having some biomarker evidence of AD (see Fig. 1). This stage is often referred to as subjective cognitive decline (SCD). SCD refers to self-reported experience of decline in cognitive function without objective impairment on cognitive assessments or daily functioning [20]. The prevalence of SCD has been suggested to range between 25% and 50% among older adults (65 years and above) [21]. Although the exact conversion rate of SCD individuals to AD remains unknown, SCD individuals have a higher risk of developing subsequent objective cognitive impairment which in turn leads to the progression to other stages of AD, and it is therefore proposed that SCD with positive AD-related biomarkers is the first symptomatic expression of preclinical AD [22–26].

The second stage is mild cognitive impairment (MCI) due to AD, which is described by impairment in cognition particularly in the memory domain and the presence of biomarker evidence for AD. MCI is regarded as the prodromal stage between normal cognitive changes accompanied with aging and the early clinical symptoms of dementia (see Fig. 1) [27, 28]. MCI is typically defined as performance below 1.5 standard deviations on cognitive assessments, matched to age, gender, and education normative data [20]. It is proposed that approximately 16% of adults over the age of 70 years have MCI [29]. The annual conversion rates from MCI to AD dementia are suggested to range between 4% and 23% in community-based samples and 10–30% in a clinic-based sample [30–33]. The third stage is dementia of the AD type, which is characterized by the presence of dementia syndrome, and is based on objective cognitive impairment and the presence of AD biomarkers (see Fig. 1) [13, 34–36]. The duration and progres-
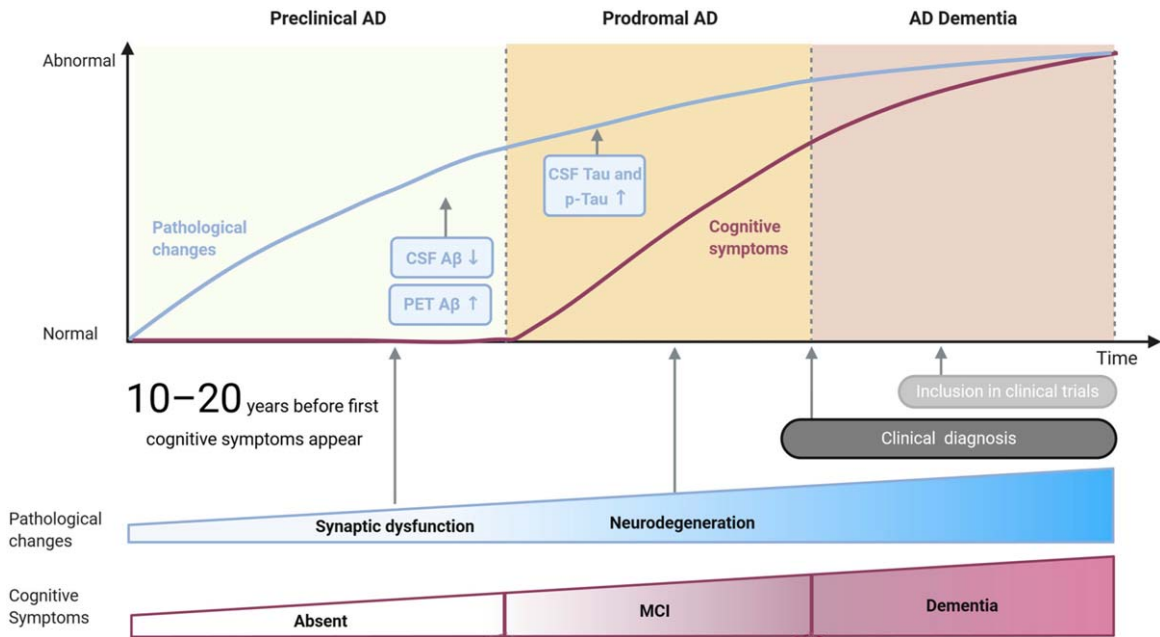
Fig. 1. Three subsequent stages of Alzheimer's disease: preclinical AD, prodromal AD, and AD dementia. Pathological changes are indicated by a blue line on the graph and at the bottom of the figure. Cognitive symptoms are indicated by a purple line and at the bottom of the figure. Aβ and tau are the pathological biomarkers currently used for AD. Adapted from [19].

sion of each of these stages is not the same in each individual and it has been proposed that factors such as age of onset, genetic risk factors, and gender play a significant role in the duration of each stage [37]. The stages before dementia due to AD, i.e., SCD and MCI, may present a target population for AD intervention as treatments at the dementia stage of the disease have shown no promise in altering the disease progression, as the is already substantial neuronal injury and cognitive decline [36]. Objectively identifying this target population may be possible by investigating and understanding the connection between AD and associated health conditions.

HEARING LOSS (AGE-RELATED HEARING LOSS)

Age-related hearing loss (ARHL), also known as presbycusis, is the most prevalent health condition that affects older adults worldwide [1, 38]. It is estimated that close to a third of people over the age of 65 experience disabling hearing loss [1]. ARHL is characterized by bilateral, progressive, high-frequency deterioration of hearing sensitivity that is associated with aging [39]. ARHL is also characterized by impaired sound localization, reduced central auditory processing as well as reduced perception and under-

standing of speech in noisy environments [40]. The development of ARHL is suggested to be multifactorial, influenced by factors such as cochlear aging [38, 41], noise exposure [42, 43], gender [44], race [45, 46], genetic predisposition [47], environmental variables [48, 49], hypertension [50], and other health comorbidities, such as type 2 diabetes [51]. The main pathologies of ARHL are of cochlear origin, including loss of sensory (hair) cells, stria vascularis atrophy, auditory nerve degeneration, and loss of spiral ganglion neurons, and often coupled with changes in central auditory pathways [40, 52].

ARHL has been classified into six categories: sensory, neural, strial, cochlear conductive, mixed, and indeterminate [53]. Sensory ARHL is associated with the degeneration of the basal end of the organ of Corti, in particular loss of outer hair cells, which causes hearing loss in high frequencies [38, 43]. Neural ARHL, which is characterized by diminished speech discrimination, is suggested to be a result of spiral ganglion cell and nerve fiber loss [53]. It is suggested that loss of approximately 50% of the afferent nerves, due to cell death, results in reduced speech discrimination; however, measurable threshold changes may not be observed until over 90% of nerve fibers are lost [54, 55]. The atrophy of the stria vascularis, the secretory tissue in the lateral wall of the cochlear duct

which regulates the amount of potassium and sodium ions in the endolymph, results in reduced pure-tone thresholds at all frequencies and this is referred to as strial ARHL [38, 43, 56]. Cochlear conductive ARHL is suggested to be a result of degenerative changes that cause increased stiffness of the basilar membrane. It is often characterized by a gradual down-sloping audiogram, with low-frequency hearing loss [38]. Mixed ARHL is believed to be a result of a combination of the histopathology of other ARHL categories, while indeterminate ARHL is characterized by high-frequency hearing loss without the presence of a consistent histological appearance [38, 48].

Central brain changes due to ARHL

Neurochemical and metabolic changes in the central nervous system associated with ARHL have been observed using magnetic resonance spectroscopy (MRS). One MRS study demonstrated reduced excitatory neurotransmitter levels such as glutamate and N-acetylaspartate concentrations with increased lactate in the auditory cortex of older adults with ARHL [57]. In contrast Gao et al. [58] found that inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), concentrations were decreased in central auditory regions in ARHL participants when compared to age-matched normal hearing participants. Lower GABA concentrations have also been demonstrated in animal models of ARHL, with decreased GABA levels found in both the auditory cortex [59, 60] and the inferior colliculus [59, 61, 62].

Although pathological changes, including reduced gray matter [63–65] and white matter [66, 67] volumes, can accompany healthy aging in the central brain regions, a more pronounced decrease in gray and white matter volume in the auditory cortex has been reported in ARHL patients in comparison with healthy age-matched controls [49, 68–70]. In relation to ARHL, reduced gray matter volume has also been observed in multiple brain regions, including the temporal lobe [44], particularly the superior and middle temporal gyri [68], medial and superior frontal gyri [68], hypothalamus [71], and occipital lobe [71]. Changes in these brain regions and neural networks are associated with impaired cognitive functions including episodic visuospatial memory and learning memory [72, 73], working memory and executive functions [74], attention switching [75], and verbal recognition memory [73]. Additionally, the cingulo-opercular cortex has been shown to be atrophied in individuals with ARHL as well as in those with impaired episodic memory [45]. Furthermore, one MRI study revealed that whole brain volume is reduced in participants with ARHL in comparison to healthy age-matched controls [76]. Collectively, these findings suggest that cochlear dysfunction is linked with cortical changes in regions involved in cognitive functions [45, 47].

Diffusion tensor imaging (DTI) studies in people with hearing loss have revealed changes in the white matter tracks in different regions of the auditory pathway [68, 77]. DTI is used to investigate white matter tracts *in vivo* and to quantify the directionality of water diffusion in order to yield an index of microstructural integrity [78]. Fractional anisotropy values, a measure of connectivity derived from DTI, have been shown to be reduced in the lateral lemniscus, inferior colliculus, the superior olivary complex, and the auditory cortex [77]. Husain et al. [68] found that the orientation of white matter tracts leading in and out of the frontal cortex and temporal cortex differed significantly between a mild-to-moderate hearing loss group in comparison to a normal hearing group. Alterations to the white matter tracts may be attributed to sensory deprivation resulting in axonal loss or demyelination resulting in damage to white matter tracts or the extension of other fibers into the regions forming disordered white matter tracts [68]. Hence, these findings from DTI studies indicate that ARHL causes secondary changes in the central auditory pathway as well as brain regions that do not play a direct role in auditory processing.

MECHANISMS FOR THE RELATIONSHIP BETWEEN ARHL AND AD

A number of potential mechanisms have been suggested for the relationship between ARHL and AD. These mechanisms include: 1) common cause, 2) sensory deprivation, 3) occupation of cognitive resources, and 4) function and structure interaction.

1) Common cause mechanism

Common factors that may influence hearing function and cognitive function could explain the correlation between ARHL and AD. The common cause mechanisms suggest a third variable that results in impairment in both hearing loss and cognitive impairment, these include: aging, mitochondrial dysfunction, microvascular factors, and inflammation. Age-related neurodegeneration is a common feature

of cognitive aging [79], which is characterized by atrophy of multiple brain regions [80] and changes in cognitive performance [81]. Similarly, age-related changes can be seen along the auditory pathway [38, 40, 42, 52], as discussed above. Microvascular complications are common feature in both ARHL and dementia. Research suggests that diabetes mellitus, which is characterized by many microvascular complication, is a common risk factor for both hearing loss [82, 83] and dementia [3, 84].

Inflammatory pathologies have also been suggested to be another common cause for dementia and hearing loss. It has been proposed that inflammatory factors that are influenced by lifestyle factors (e.g., obesity, sleep quality, and physical activity) could be mediators in the development of AD dementia [85, 86]. Inflammatory mediators have been proposed to have harmful effects on small vessels which can result in atrophy of cortical structures critical for cognitive functions [87, 88]. Inflammatory responses that contribute to age-related pathologies have also been observes in the inner ear. While the influence of inflammatory factors on ARHL are not fully understood, there is evidence to suggest that there is an inflammatory response in the inner ear of aging mice which is induced by oxidative stress [89, 90]. Mitochondrial dysfunction is a mediating factor is oxidative stress and there are some theories that suggest ARHL and AD may be a result of mitochondrial dysfunction and changes in signal pathways.

ROS/VEGF pathway

The mitochondria play a key role in oxidative metabolism and is the primary production site for reactive oxygen species (ROS), reactive radical and non-radical derivatives of oxygen [91]. High concentrations of ROS can have toxic effects on cellular mechanisms that lead to accumulation of oxidative stress/damage, ultimately resulting in cellular dysfunction [92]. There is often an increase in ROS activity and decrease in ROS clearance with aging [93–95]. Buildup of ROS in cells has been suggested to result in mtDNA mutations and mitochondrial dysfunction which decreases the quantity of vascular endothelial growth factor (VEGF), a signaling protein, in the brain [96].

Interestingly, VEGF has been suggested to be a common feature in the molecular mechanisms of ARHL and AD. In AD patients, VEGF expression is lower in hippocampal, superior temporal and brainstem regions [96]. Due to the involvement of VEGF in vascular remodeling, endothelial maintenance, and

angiogenesis, the reduction of its levels in AD could be an indication of altered capillary function, which can modify Aβ efflux [96–98]. VEGF has also been shown to bind to amyloid plaques with high affinity, resulting in reduced availability of VEGF under hypo-perfusion conditions, in turn contributing to vascular dysfunction and neurodegeneration in AD [99].

Although there is limited information on the specific function of VEGF in ARHL, one animal study has demonstrated that cochlear VEGF expression is reduced in aged mice with ARHL, indicating that vascular abnormalities may be an influencing factor in ARHL [100]. Acoustic trauma, one of the risk factors of ARHL, has been reported to result in increased vascular permeability, changes in cochlear blood flow as well as vasoconstriction [101, 102]. In addition to this, VEGF was shown to be upregulated in spiral ganglion neurons, spiral ligament and stria vascularis following acoustic trauma [103].

SIRT1/PGC-1a pathway

Peroxisome proliferator-activated receptor γ coactivator 1 (PGC-1α), the primary regulator of mitochondrial biogenesis, is thought to play a role in impeding neurodegeneration [67]. PGC-1α has been shown to avert the neurodegenerative effects of 1-methyl-4-phenyl-1, 2, 3, 6- tetrahydropyridine (MPTP) as well as increase ROS detoxification [72]. In cultured hippocampal neurons, PGC-1α has been found to support synaptogenesis and spinogenesis [78]. SIRT1 (silent information regulator 2 homolog 1), a nicotinamide adenine dinucleotide-dependent histone deacetylase, induces adaptive response to metabolic stress and can deacetylate PGC-1α [72, 75]. Deacetylation of PGC-1α results in an increase in its transcriptional function, which is essential for the activation of mitochondrial fatty acid oxidation genes [75, 77].

Age-related reduction in SIRT1-PGC-1α expression has been suggested to cause hair cell apoptosis and neural degeneration due to impaired mitochondrial respiratory function, leading to ARHL. An animal study demonstrated reduced SIRT1-PGC-1α expression in the cochlea of aged mice [38]. Additionally, an *in vitro* experiment demonstrated that when SIRT1 expression was increased, PGC-1α expression was increased in cochlear hair cells which inhibited cell apoptosis and promoted cell proliferation [38]. Therefore, the SIRT1-PGC-1α pathway is thought to play a major role in the pathogenesis of ARHL. Concurrently, impaired function of the SIRT1-PGC-

1α pathway in the brain has also been found to alter the expression of β-secretase 1 (BACE1), which in turn alters AβPP cleaving resulting in Aβ production. Wang et al. [39] demonstrated, using both *in vivo* and *in vitro* experiments, that reduced expression of PGC-1α caused altered expression of BACE1, while overexpression also reduced BACE1 expression. Altered expression of BACE1 contributes to the production of Aβ in the brain and to incidence of AD. Although more research is needed, the SIRT1-PGC-1α pathway has been suggested as a potential treatment target to prevent individuals with ARHL from developing AD [104].

2) Sensory Deprivation Mechanism

Sensory degradation in hearing impaired people has been suggested as another mechanism for the relationship between ARHL and AD. Due to hearing loss, there is degradation and loss of input to the cortex [105]. Progressively, this degradation of sensory information results in changes to the function and structure of auditory and cognitive systems in the brain [106–108]. Prolonged sensory deprivation due to peripheral ARHL may lead to decreased cortical volume similar to that seen in cognitive decline [19, 76]. A number of brain regions, including the superior temporal lobe [68, 109], frontal lobe [68, 110], and hippocampus [111], show reduced gray matter density with ARHL. These brain regions play an important role in semantic memory and are involved in advancement along the dementia continuum [68]. Degraded auditory sensory information has also been linked to a number of functional changes, including decreased memory and comprehension of spoken language, impaired speech-in-noise performance, as well as cognitive impairment [105, 107, 112]. Functional changes, such as impaired speech-in-noise processing, have also been associated with reduced social interaction leading to social withdrawal and isolation [113, 114], which are also suggested to be a risk factors in dementia [115, 116] (see Kuiper et al. [117] for a review).

There is also evidence to suggest that ARHL is associated with decreased white matter volume and microstructural integrity in brain regions essential for cognitive function, such as the temporal lobe [70, 118, 119]. Additionally, cross modal reorganization, which is the recruitment of cortical resources from the deprived modality (i.e., auditory) by un-impacted modalities, due to ARHL can be seen in those with early stages of cognitive impairment [120, 121]. In other words, the structural and functional changes seen in ARHL result in additional restriction of cortical resources accessible for cognitive processes [122, 123]. However, the length of sensory deprivation, critical age of HL onset and degree of cortical reorganization that is necessary to induce structural brain changes, brain atrophy and impaired cognitive function remains unclear.

3) Occupation of Cognitive Resources Mechanism

The occupation of cognitive resources mechanism suggests that the association between ARHL and AD is a result of higher cognitive processing that is necessary to compensate for the degraded sensory input. A greater amount of neural resources, i.e., working memory, language processing and attention, must be allocated to auditory processing when auditory input is degraded [122, 124]. This results in less resources available for higher cognitive processing, including memory retention and retrieval [122, 123]. Imaging studies demonstrated that brain activation patterns are altered when processing challenging tasks, which would mean that as auditory processing and listening become more challenging, brain activation patterns change [122, 125, 126]. Furthermore, individuals with hearing loss have decreased gray matter density in the primary auditory cortex and reorganization of processing systems when sensory auditory stimulation is reduced [127].

Dual-task paradigms have been adopted to examine whether difficulty in listening results in decreased cognitive resources available for other tasks [128]. These dual-task paradigms are attentionally demanding, signifying an attentional basis by which the occupation of cognitive resources of listening may impact memory function in AD [122]. It has been demonstrated that listening to speech in noise results in decreased performance in secondary non-auditory cognitive tasks [128]. In addition to this, replicating the challenges of listeners with hearing loss by degrading or masking speech results in impairment in subsequent cognitive task performance [128]. Functional imaging studies demonstrated that the auditory cortex, left inferior frontal lobe, and hippocampus are involved in speech perception in challenging listening conditions [129, 130]. Behavioral data provide evidence for the use of greater cognitive resources in the presence of sensory degradation [128] and imaging studies indicate the involvement of a wide network of brain regions in difficult listening condi-

tions [130–132]. Therefore, cognitive function may decrease in hearing impaired adults due to the occupation of cognitive resources when processing degraded sensory information [133].

4) Function and Structure Interaction Mechanism

Expanding on the previously outlined mechanism, another mechanism involving both cognitive resource occupation (neural activity) and AD pathology has been proposed for the relationship between ARHL and AD. This mechanism suggests that hearing loss modifies cortical activity in the medial temporal lobe (MTL), which can be interrelated to AD pathology in the same region. The MTL plays an important role in memory processing and episodic memory [134, 135]. It is comprised of several sub-regions including the hippocampus, the parahippocampal cortex in the posterior parahippocampal gyrus, and the perirhinal and entorhinal cortices in the anterior parahippocampal gyrus [134, 136–138].

Neurofibrillary changes, as a result of tau protein hyperphosphorylation, have been suggested to best correlate with the cognitive symptoms of AD [139]. The earliest AD related neurofibrillary changes have been found in MTL regions [140, 141]. It is suggested that hearing impairment can cause altered neuronal activity in MTL structures, which in turn can cause or increase AD neuropathology [122]. Studies have demonstrated that the hippocampus, a sub-region of the MTL, plays a critical role in the memory of sound in trace conditioning tasks [142]. The hippocampus has also been shown to be active during other types of sound processing, including pattern recognition from a random sequence [143], statistical learning of tone streams [144], and auditory working memory during investigation of acoustic patterns that change over time [145]. In addition to this, there is research to support the role of the hippocampus in the processing of degraded speech [130, 131].

Speech-in-noise perception has been associated to cognitive skills, including phonological working memory and auditory working memory [146]. It is suggested that auditory information with similar properties can be connected by working memory to enable the filtering of central information of interest during speech-in-noise listening [122]. Degraded auditory signals caused by hearing loss can impact speech-in-noise performance, which in turn causes auditory pattern analysis and auditory working memory mechanisms to work harder as separation of speech from noise becomes more difficult [130, 131,

146]. This eventually results in elevated neural activity in the MTL [122]. Furthermore, gradual hearing loss has also been suggested to result in widespread reorganization of plasticity-related neurotransmitter expression. Cortical and hippocampal expression of glutamate subunits of the NMDA receptor have been shown to increase in adult mice that have hearing loss in comparison to control mice that lack auditory deficits [147]. Significantly impaired hippocampal synaptic plasticity and compromised function are also suggested to be accompanied by memory impairment [147].

Similar to hearing loss, pathological markers of AD, tau and Aβ, have been suggested to induce alterations in glutamatergic [148–150] and GABAergic [151] function, resulting in altered synaptic activity and disrupted neural connectivity in neurocognitive networks. Human studies have shown the co-localization of elevated neural activity and tau deposition in AD, particularly in parietal and occipital brain regions [152, 153]. In addition, an animal study has suggested a direct relationship between higher neural activity and AD pathology, including Aβ. Bero et al. [154] provided evidence that suggests neuronal activity regulates regional concentrations of interstitial fluid Aβ which in turn drives local Aβ accumulation. Therefore, some brain regions, in particular those with increased neuronal activity, can be more vulnerable to Aβ deposition in AD [154]. The insight that neuronal activity may play a contributing role in the development of AD may have implications for early diagnosis and treatment strategies.

OTHER MEDIATING FACTORS IN THE RELATIONSHIP BETWEEN ARHL AND AD

The link between hearing impairment and cognitive dysfunction could also be partly mediated by other risk factors for dementia, which include social isolation and depression. Studies have found that hearing loss was linked to increased loneliness and social isolation with both being negatively correlated with cognitive function [113, 155]. Furthermore, individuals with ARHL have been suggested to have an increased the risk developing depression later in life [156]. Depression is considered to be an autonomous risk factor or prodromal symptom of dementia and AD [3], with the co-occurrence of ARHL and depression further increasing the possibility of developing cognitive impairment associated

with dementia [156]. Although the influence of these mediating factors on the above-mentioned mechanisms is yet to be determined, there is potential for the co-occurrence of multiple risk factors of dementia to be a greater indicator of those at increased risk of developing dementia.

FUTURE DIRECTIONS

Hearing loss intervention as a possible treatment or prevention for AD

The possibility of hearing restoration altering the risk of developing AD or stopping/reversing cognitive decline depends on which, if any, of the postulated mechanisms are correct. In the case of the association between ARHL and AD being due to common cause (mechanism 1), restoration of hearing would have no effect on the progression of dementia or result in any improvement of cognitive function. If the sensory deprivation mechanism is true, restoration of hearing would reduce the risk of dementia, however, would not reverse cognitive impairment. On the other hand, if the association between ARHL and AD is caused by the cognitive resource mechanism (mechanism 3), the increased load of cognitive resources could be reversed by treating ARHL. This should, in theory, reduce the risk of developing AD and restore a degree of cognitive function regardless of the stage of the disease [122]. Finally, if the fourth (function and structure interaction) mechanism is true, early identification and treatment of hearing impairment could delay or prevent neurodegenerative changes caused by altered sensory input and slow progression of structural changes at later stages of cognitive decline. The risk of further cognitive decline would rely upon the duration and severity of hearing loss prior to treatment. That is, if the duration between initial hearing loss and the treatment of hearing impairment is too long, the chain of structural changes may have already begun and could continue, although at a slower rate, to cause future cortical degeneration that would lead to AD [122]. Looking into some of the previous research on the impact of treating ARHL on cognitive function, could provide some insight into which mechanism is more likely.

It has been suggested that the rehabilitation of hearing loss, using hearing aids (HA) or cochlear implants (CI), can have a positive impact on cognitive dysfunction. However, research on the use of HA and CI as a possible treatment or prevention for cognitive decline has yielded mixed results. Previous research comparing cognitive function over a 12-month period between CI recipients and CI candidates showed that hearing rehabilitation improved a variety of cognitive functions, including working memory and strategy use [157]. Mosnier et al. [5] also demonstrated improved cognitive function in patients 12 months following cochlear implantation in addition to improvements in speech perception and quality of life. On the other hand, another study investigating the impact of CI on cognitive ability in older adults with profound hearing loss found no significant improvements in cognitive function 18 months after receiving a CI [6]. However, this study did demonstrate that ARHL and age were correlated with significantly decreased executive function and visual attention before receiving a CI [6].

A recent pilot study on participants with hearing loss has found that HA users had significantly better performance when compared to non-HA users on a working memory task (delayed matching-to-sample test) [158]. Additionally, a population-based longitudinal cohort study, investigating episodic memory function in 2,040 individuals before and after HA use, revealed that HA use resulted in a reduction in the rate of episodic memory decline [4]. These results indicate that ARHL treatment could have a positive impact on age-related cognitive decline. Similarly, Bucholc et al. [159] found in a longitudinal population based study of 2,114 MCI participants with HL that used HA had a significantly lower risk of developing all-cause dementias in comparison those who were non-HA users.

However, in contrast to this, a pilot study on participants with ARHL and primary dementia indicated that HA use did not improve cognitive function or psychiatric symptoms [160]. This suggests that hearing rehabilitation at more severe stages of cognitive decline may be ineffective in improving cognitive function; however, it is noteworthy that this pilot study was conducted over a short 24-week period and had no comparison group, limiting the validity of the conclusions [160]. Similarly, a randomized controlled trail investigating the efficacy of HA use on cognitive function in individuals diagnosed with AD found no significant impact on cognitive decline following 6 month of HA use [161]. Additionally, van Hooren et al. [162] investigated the impact of HA use on cognitive functions in participants without neurological diseases. They found that cognitive functions, including attention and memory, did not improve in HA users in comparison to non-HA users after a 12-month period.

Interestingly, a recent study by Cuoco et al. [163] found that 6 months of HA use has positive implications on cognitive function in participants with mild-HL but not at more severe-HL. The authors suggest that hearing rehabilitation in those with mild-HL may be more effective at delaying cognitive decline; however, a longer follow-up period and further research would be needed to fully understand the effect HA use can have in those with more severe-HL [163]. Additionally, treating HL using HA or CI have been found to have positive impacts on mental health and result in substantial improvement in quality of life in adults with HL [164–166]. Collectively, the research above indicates that treating ARHL may not reverse cognitive decline; however, the rate of decline and the risk of dementia may be decrease and the quality of life may be improved. For this reason, it is suggested that the fourth mechanism, function and structure interaction, is the more plausible theory for the relationship between ARHL and AD.

HEARING ASSESSMENTS AS A POSSIBLE DIAGNOSTIC/SCREENING TOOL FOR AD

In view of the link between ARHL and cognitive decline, the question has been raised whether auditory tests could be used to detect changes in cognitive function.

Behavioral auditory assessments

Central auditory processing (CAP) refers to the integrated neural processing of auditory signals in the central auditory nervous system [167]. Behavioral CAP assessments are used to measure the functional abilities of the auditory system; these tests include auditory discrimination, auditory temporal processing, dichotic listening, monaural low-redundancy speech, and binaural interaction tests, described in more detail by the American Academy of Audiology [167]. Multiple studies have examined the use of behavioral CAP tests as a potential tool to identify cognitive dysfunction associated with AD [168–173].

Age-related CAP dysfunction has been suggested as an indicator for increased risk of cognitive impairment and AD [174, 175]. Dichotic listening assessments, which assess the ability to separate or integrate different auditory stimuli presented simultaneously to each ear, have been proposed to involve cognitive processes, including memory and attention, as neuroimaging studies have shown activation in the frontal, parietal, and temporal lobes in individuals during performance of these tasks [176, 177]. Indeed, studies evaluating central auditory function in cognitively impaired older adults using Dichotic digits test (DDT) [173, 178] and dichotic sentence identification test (DSI) [168, 173, 178] have shown poorer performance in these tests in the cognitively impaired group in comparison to healthy age-matched controls. This could be related to the fact that individuals with AD frequently have impaired executive functions, causing an inability to respond correctly in the dichotic listening task when instructed to maintain attention to a particular ear [176, 179]. Poorer performance in the DSI test has also been proposed to be a predictor of reduced cortical thickness in the middle frontal gyrus, a region associated with cognitive process such as episodic and working memory [180].

Temporal auditory processing, the ability to analyze acoustic events over time, has also been suggested to be impaired in people with cognitive decline [168, 181]. Temporal auditory processing assessments have been proposed to involve and reflect cognitive functions, such as attentive executive function and memory, as they involve information integration from both hemispheres across the corpus callosum in order to identify and process sequences of auditory patterns [168, 181, 182]. Additionally, diminished speech perception in noise, as tested using synthetic sentence identification-ipsilateral competing message (SSI-ICM) and speech perception in noise test (SPIN), has also been associated with cognitive impairment [170, 173, 183]. Performance on the SSI-ICM test has been proposed to be influenced by the cortical thickness of the parahippocampal gyrus and entorhinal region and interestingly both regions are susceptible to atrophy in pre-symptomatic phases of AD [9]. Furthermore, cortical thickness in the inferior parietal lobe and primary auditory cortex has also been suggested to influence SSI-ICM performance [9, 184]. Reduced performance in the SSI-ICM test has been observed in people with MCI and AD, indicating that sensory integration and auditory processing are impaired in those with AD related cognitive decline [168, 173, 181]. Interestingly, SSI-ICM test performance has also been shown to be significantly poorer in people with SCD in comparison to those without SCD [185]. While more research is needed to fully establish the reliability and accuracy of SSI-ICM in differentiating between SCD and non-SCD participants, there is evidence to suggest that this CAP test could have the potential to identify probable pre-clinical AD.

Although impairment in central auditory function is seen in those with cognitive impairment, the use of subjective or behavioral central auditory tests as a possible screening tool for AD has to be carefully considered due to a number of reasons. Firstly, there are a limited number of studies that have investigated CAP in cognitively impaired individuals using behavioral testing. This could be due to the complexity of these behavioral tests and difficulty to conduct in people with cognitive dysfunction. Behavioral CAP tests require substantial attention, understanding, intricate responses and active participation from the individuals, which limits their applicability and reliability in those with moderate to severe cognitive impairment. Additionally, other health related factors could influence the performance of an individual on these behavioral auditory tests, such as visual, physical, mental, and psychological factors [167, 186, 187]. Importantly, hearing loss can also influence the results of behavioral CAP testing and hence these tests cannot be used for older adults with moderately-severe or profound hearing loss [187, 188]. Finally, as many of the behavioral CAP tests cannot be conducted in free field settings, it would not be possible to perform these tests on individuals with hearing aids or cochlear implants [167].

Objective auditory assessments

Objective methods of measuring central auditory function have been proposed to overcome the clinical limitations associated with behavioral CAP tests outlined above. Auditory electrophysiology provides an objective measure of auditory function with little to no participation required from the listener. It is the measure of auditory event-related potentials (AERP), which reflect the variations in electrical brain activity in response to a particular task/or stimulus [189]. Distinct peaks within the AERPs, presenting at different latencies, represent neural activity from various anatomical locations throughout the auditory pathway and associated brain structures [190]. Some AERPs have been shown to reflect cognitive functions such as auditory memory [191], attention [192, 193], working memory [191, 194], language comprehension [195], discrimination [196] as well as decision-making [197].

AERPs can be divided into early latency, middle latency, and late latency responses, described in more detail by Niedermeyer et al. [198]. Some studies indicate that auditory brainstem responses (ABR), which are early latency responses, are prolonged in participants with AD with normal hearing thresholds, which suggests brainstem and midbrain abnormalities in individuals with AD related cognitive impairment [199, 200]. However, other studies report no differences in ABR measures in people with AD [201, 202] or MCI [203] in comparison to healthy age-matched controls. Disease severity and the duration of the disease have been suggested to contribute to the conflicting results seen across ABR studies, which could limit the reliability of ABR measures to differentiate between healthy and cognitively impaired older adults, particularly at early stages [199].

A recent meta-analysis reported that higher processing of sensory information, as reflected by late latency AERPs N100 and P200, are impaired in those with AD when compared to healthy controls [204]. The N100 and P200 have been proposed to be produced by the primary and secondary auditory cortex, hence, changes in the appearance of these responses are thought to reflect measurable impairments in processing and perceiving variations in an auditory information [205, 206]. Similar to results observed in behavioral CAP tests, particularly SSI-ICM, objective measures of discrimination, perception, and classification of auditory signals using N200 latency have also been shown to be delayed in those with cognitive impairment associated with AD [196, 204, 207]. The neural generators of the N200 peak include the auditory cortex and thalamic region [208, 209] and significant delays in the N200 latency have been observed in participants with MCI and those with AD [204, 207].

The P300, another late latency cortical AERP, is the most widely studied AERP for cognitive function. Research has suggested that this response is altered with the development of neurodegenerative diseases, showing as reduced P300 amplitude and increased P300 latency in those with cognitive impairment associated with AD compared to healthy controls [204, 210, 211]. Multiple brain regions have been associated to the generation of the P300 response and these include the temporal parietal junction, medial temporal lobe, frontal lobe, and parietal cortex [212, 213]. These brain regions are well known to play a role in sensory processing, cognitive function, memory storage, and executive functions. Therefore, P300 is proposed to reflect cortical activity as it is dependent on functions including discrimination, attention, and memory in order to be elicited. A meta-analysis revealed that those with MCI and AD have significantly longer P300 latencies in comparison to healthy age-matched controls [204], indicating dys-

functional attention-driven discrimination processing and reduced classification speed in task processing in those with cognitive decline associated with AD [193, 194]. Although multiple meta-analyses indicate that P300 latency measures do not significantly differ between MCI and AD participants [204, 214], a longitudinal study found that MCI participants that developed probable AD after a 5-year period had significantly longer baseline P300 latency in comparison to MCI participants that did not go on to develop AD [215]. These findings imply that P300 latency measures could be beneficial in the objective detection of people at prodromal stages of AD. Unfortunately, to date, no study has examined AERP measures in those with SCD, which highlights the need for further research in order to evaluate the reliability and usefulness of these measures as an early biomarker of AD. Investigating AERP measures in those with SCD could aid in identifying people at higher risk of developing dementia, years prior the appearance of clinical features of AD [20].

CONCLUSION

Impaired auditory function may be a valuable marker of preclinical stages of cognitive impairment. Multiple potential mechanisms have been suggested for the association between impaired auditory function and cognitive impairment. All four mechanisms mentioned in this paper demonstrate the intricate relationship between auditory and cognitive function. We suggest that the fourth mechanism, function and structure interaction, is the more plausible theory for the association between ARHL and AD. The insight that altered neuronal activity due to ARHL, as suggested by the fourth mechanism, may play a causal role in AD can be beneficial for early detection and treatment strategies. There is evidence to suggest that early identification and treatment of auditory impairment could delay or prevent neurodegenerative changes due to altered sensory input and slow progression of structural changes at later stages of cognitive decline. While this review provides interesting insights into the relationship between ARHL and AD, it is important to note that considerably more research is needed for a cause effect to be established. Nevertheless, investigating the role of auditory markers for identifying cognitive related brain changes in individuals at high risk of developing AD would help improve understanding of the underlying mechanisms for the link between ARHL and

AD hopefully enabling the development of effective interventions.

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