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Opinion

Which Came First, Age-Related Hearing Loss with Tinnitus or Cognitive Impairment? What are the Potential Pathways?

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Abstract

Research on the causal relationship between age-related hearing loss (ARHL) and/or tinnitus and dementia is an important and fast-moving field. In this opinion paper, the up-to-date evidence and potential mechanisms for the bidirectional relationship are reviewed. We also present several critical factors that increase the challenges of understanding the causal relationship. These factors include common causes (such as aging, frailty, vascular impairment, and chronic inflammation), auditory and cognitive reserves, and the difficulty in distinguishing central auditory processing disorder (CAPD) from cognitive impairment. Finally, based on cumulative evidence, we propose an integrated mechanism in which the central auditory system might be the common target of both peripheral auditory impairment and dementia or its precursor. There is a bidirectional interaction between the peripheral and central auditory systems and between the central auditory systems and the cognitive brain. CAPD causes the depletion of auditory and cognitive reserves, and indirectly affects the peripheral auditory system via the auditory efferent system. According to the proposal, multimodal intervention might be beneficial for patients with ARHL and/or tinnitus and cognitive impairment, apart from hearing restoration by hearing aids or cochlear implants.

Keywords: auditory reserve; cognitive impairment; cognitive reserve; dementia; frailty; hearing loss; hearing restoration; multimodal intervention; tinnitus

1. Evidence for a Bidirectional Association between Age-Related Hearing Loss, Tinnitus, and Cognitive Impairment

1.1 The Association of Age-Related Hearing Loss with Tinnitus and Cognitive Impairment

Age-related hearing loss (ARHL), caused by peripheral hearing loss or central auditory processing disorder (CAPD), is the third leading cause of chronic disability in the older population [1]. ARHL is one of the most important modifiable risk factors for dementia [2,3]. Cumulative evidence links peripheral ARHL and cognitive decline with impaired performance across multiple cognitive domains, including episodic memory and processing speed [4]. An independent association was also observed between subclinical hearing loss and cognitive impairment in a cross-sectional population study [5]. A longitudinal cohort study further indicated that subjects with worse subclinical hearing loss have a steeper cognitive decline, as measured by the Digit Symbol Substitution Test over a mean follow-up of 9.1 years [6]. However, a direct causal effect of peripheral hearing loss on dementia with hearing alterations is not defined. In a large cohort of cognitively healthy older people, peripheral hearing dysfunction was not associated with the pathological hallmark brain amyloid deposition of Alzheimer's disease (AD), the main phenotype of dementia [7]. Age-related CAPD may precede the onset of clinical dementia in people with probable AD and might be an early marker of mild cognitive impairment (MCI) and AD [8,9]. Older individuals with CAPD had a high risk for the subsequent onset of probable AD [10,11], and CAPD was independently associated with cognitive frailty [12], a frailty phenotype defined by coexisting physical frailty and MCI.

Chronic subjective tinnitus is associated with poorer performance in multiple cognitive domains, such as executive function, attention, processing speed, general short-term memory, and general learning and retrieval [13–15]. Although ARHL and noise exposure are the most common causes of chronic subjective tinnitus, the number of studies on cognitive dysfunction in older patients affected by chronic tinnitus is limited. ARHL with tinnitus [16–18] or chronic subjective tinnitus alone [19] were independently associated with MCI. Other studies indicated no association between chronic tinnitus and cognition in older individu-

als [17,20–22]. The presence of tinnitus in non-Hispanic participants with hearing loss was even associated with improved cognitive performance [20]. The severity of cognitive impairment or cognitive frailty was also positively associated with the severity of ARHL and/or tinnitus [23]. Hyperacusis, a precursor of tinnitus, is another common auditory problem and is associated with depression in older subjects [24]. Nevertheless, the number of studies on cognitive dysfunction in older individuals affected by hyperacusis is minimal.

1.2 The Associations between Cognitive Impairment Due to Dementia and Central Auditory Processing Disorder

Accumulating evidence suggests that neurodegenerative pathologies add disproportionate central hearing deficits to any already existing peripheral hearing loss [25–27]. Clinical findings have indicated that central auditory processing is impaired in people diagnosed with AD and its preclinical stages and may manifest many years before clinical diagnosis [26–28]. Patients with semantic dementia frequently reported tinnitus and hyperacusis and were found to have abnormal neuroanatomical alterations in cortico-subcortical auditory and limbic networks [29]. The prevalence of auditory hallucinations in Parkinson's disease and in dementia with Lewy bodies is estimated to be 8.9% and 30.8%, respectively [30]. Neuropathological findings have indicated that AD pathological hallmarks, i.e., amyloid plaques and neurofibrillary tangles (NFTs), presented in the higher structures of the central auditory pathways, including the central nucleus of the inferior colliculus, the ventral division of the medial geniculate body, and primary and secondary auditory cortical areas, but did not in the cochlea and cochlear nucleus [31]. CAPD was persistently associated with cerebrospinal-fluid (CSF) tau levels, entorhinal and hippocampal cortex volumes, cortical thickness, and cognitive deficits in cognitively and physically healthy individuals with positive AD family history [9]. These neuropathological alterations suggest that AD-related CAPD might not have resulted from peripheral hearing loss and induced maladaptive plastic changes.

2. Which Came First, Age-Related Hearing Loss, Tinnitus or Cognitive Impairment?

Does existing ARHL with tinnitus cause cognitive impairment, AD, and non-AD dementia? Or does exist cognitive impairment precipitate hearing loss? Understanding the relationship between ARHL, or ARHL, with tinnitus, and cognitive impairment is a critical challenge for the management of these conditions. In this opinion paper, in order to comprehend fully the advance of the relationship between age-related hearing loss (ARHL) and/or tinnitus and cognitive performance, and potential pathways, we searched PubMed for important articles published in English up to April 2023, with priority to systemic reviews and studies published in the past 5 years. The search terms include "ARHL and cognition", "ARHL and/or tinnitus and cognition", "peripheral hearing loss, CAPD, and cognitive impairment or AD or dementia or neurodegenerative diseases", "auditory and cognitive reserves", "hearing restoration and cognitive performance", and "frailty and ARHL and/or tinnitus". We also sought previous publications with high-quality research evidence from the identified papers.

2.1 Hypotheses Regarding the Causal Relationship

Several hypotheses of possible etiological mechanisms have been proposed that elucidate these relationships [32–34]. The common-cause hypothesis involves neurodegenerative, metabolic, and vascular pathophysiological alterations and chronic systemic inflammation during aging. (a) Reported hearing loss in cognitively normal individuals was associated with increased neurofibrillary tangle (NFT) burden. (b) Impaired hearing in subjects with cognitive impairment was associated with microinfarcts [35]. (c) A longitudinal study showed that ARHL might accelerate CSF tau levels and brain atrophy, and the effect was more significant in the non-demented stage [36]. (d) Vascular and/or metabolic dysfunction may contribute, in part, to the temporal coincidence of ARHL, or ARHL with tinnitus and cognitive impairment. (e) Subclinical atherosclerosis in midlife was associated with worse hearing in older adulthood [37]. (f) Components of the metabolic syndrome were positively correlated with the incidence of sensorineural hearing loss [38]. (g) Carotid artery atherosclerosis is an independent risk factor for the development of cognitive impairment [39]. (h) Both diabetes mellitus and metabolic syndrome co-existing with MCI were associated with an increased incidence of dementia [40]. (i) Mitochondrial damage, oxidative stress, and chronic systemic inflammation are also potential common underlying mechanisms of ARHL with tinnitus and cognitive impairment [10,41–44]. Based on this hypothesis, hearing intervention by hearing restorative devices to improve hearing function does not contribute to the prevention of cognitive impairment.

The cognitive-reserve depletion or cascade hypothesis is based on brain experience-dependent neuroplasticity, cognitive reserve, and brain reserve, which refer to individual differences in the functionality and structure of the brain. (a) Active listening experiences can improve brain, auditory and cognitive reserves by shaping structure brain development, neural auditory processing and perception, and hippocampal function [45–48]. (b) Environment enrichment (EE) also enhances brain and cognitive reserves in experimental mice [49]. (c) In contrast, an impoverished environment due to hearing loss causes social withdrawal, loneliness, and poor verbal communication. A longitudinal study indicated that midlife hearing loss results in greater volume decline in the entorhinal cortex and hippocampus [50]. (d) Recovering hearing input by the use of hearing restorative devices (hearing aids and cochlear implants) could decrease long-term cognitive decline, the rate

of progression to dementia, and short-term cognitive performance [51,52]. (e) Hearing rehabilitation was proposed for breaking the cascade from social withdrawal to the decline of neurocognitive functioning by the improvement of brain, auditory, and cognitive reserves. However, cognitive impairment hindered the benefits of hearing rehabilitation by hearing aids in hearing loss [53].

The cognitive-load hypothesis proposes that individuals with hearing loss use greater cognitive resources for listening to degraded auditory signals and auditory perceptual processing, which makes these resources unavailable for other cognitive tasks, eventually leading to cognitive reserve depletion [32–34]. Cognitive load may also create a burden when tested with cognitive screening tools. Patients with hearing loss tend to perform worse in standard cognitive screening tools due to their hearing difficulty in processing the target test words. Behavioral evidence indicates that hearing loss decreases the cognitive resources available for other cognitive tasks, which is observed in many dual-task interference tests [54].

Another hypothesis is proposed to further explain the neuropathological basis of cognitive load resulting in a vicious cycle of brain structure alterations, cognitive reserve and auditory reserve depletion. The hypothesis proposes a mechanism for the interaction between the medial temporal lobe (MTL) related to auditory processing and dementia pathology, which could explain the association between hearing loss and cognitive impairment [34]. There is an anatomical connectivity between the central auditory system and limbic system, including the hippocampus and amygdala [55]. MTL, especially the perirhinal cortex structures, has a strong functional association with the hippocampus, and the earliest AD pathology and NFT changes are found in these structures [56]. Decreased afferent input due to hearing loss is hypothesized to contribute to hyperexcitability in cortical activity relative to the concomitant decline in the levels of γ-Aminobutyric acid (GABA), an inhibitory neurotransmitter, and a compensatory increase of central gain (increased output activity relative to reduced input) [57]. The elevated neuronal activity in MTL might cause or increase AD pathology and neurodegeneration by N-methyl-D-aspartic acid (NMDA) receptor-mediated excitotoxicity [34]. Therefore, early hearing restoration could break the vicious cycle of cognitive overload and cognitive depletion and reduce neuronal- activity-induced dementia pathology in the MTL and hippocampus.

2.2 The Auditory Brain Links Hearing Impairment to Cognitive Impairment

Johnson and colleagues [58] proposed a model in which deficits of peripheral and central hearing and more general cognitive functions are likely to interact strongly to produce 'vicious cycling'. Peripheral hearing loss affects auditory cognition in the auditory brainstem and auditory corticalex, which link the auditory brain processing networks. The pathologies from neurodegenerative diseases lead to central hearing deficits and auditory cognitive dysfunction through auditory brain processing networks. The auditory brain links hearing impairment to cognitive decline. Alterations in central hearing or auditory cognition may constitute an early warning signal of incipient dementia due to the computational demands imposed by listening in challenging everyday acoustic environments.

3. Critical Challenges

Given that ARHL and dementia have a long, insidious, preclinical development stage, in which both hidden hearing loss and preclinical MCI are not detected by clinical examination, it is difficult to establish a temporal order or rule out shared etiologies. It is also difficult to discriminate CAPD from cognitive impairment because central auditory function is actually one of the components of cognitive performance [10,32,33]. Individuals with hearing loss are less likely to complete cognitive testing; the missing cognitive data due to hearing impairment could misestimate the ARHL-cognition relationship [59]. More importantly, systemic physiological reserve *vs*. auditory and cognitive reserve, and environmental factors, play critical roles in the relationship between ARHL with tinnitus and cognitive performance.

3.1 Systemic Vulnerability Modifies the Association

Vulnerability, or frailty status, is referred to as the decline of multiple physiological reserves to below a clinical threshold due to minor stressors; the level is insufficient to maintain homeostasis by allostatic regulation systems, leading to adverse health-related outcomes. Therefore, frailty increases the risk for ARHL with tinnitus and cognitive impairment and contributes to their relationship [10,11,43,60]. Frailty and cognitive impairment might share similar biological pathways [61]. Stress, such as environmental, physiological (above mentioned vascular or metabolic dysfunction), and psychological factors, and from unhealthy lifestyles, has been shown to be associated with cognitive [62] and auditory dysfunction [63,64]. Some stressors, such as aging, noise, and ototoxic drug exposure, not only increase the vulnerability of auditory reserve but also increase the risk of systemic vulnerability, including those of the cognitive, psychological, and multiple physiological systems. Although cumulative evidence from animal studies has indicated that these stressors could cause the decline of auditory and cognitive performance and AD-like and neurodegenerative pathological alterations in the auditory system and hippocampus, these research designs obviously could not explain the causal relationship between ARHL with tinnitus and cognitive performance [65–69].

3.2 Interactions between Environmental Factors and Auditory and Cognitive Reserves Modify the Association

Auditory and cognitive reserves are dynamic and are modified by environmental factors [43]. The intrinsic struc-

Table 1. Pros and cons regarding the hypothesis of association among age-related hearing loss (ARHL), tinnitus, and cognitive impairment.

Pros	Cons
Hearing loss is a modifiable risk factor for dementia [2,3,10]	Peripheral hearing loss does not link with brain amyloid deposition in AD [7]
Peripheral ARHL links with cognitive decline, including multiple cognitive domains [4]	Chronic subjective tinnitus is not associated with cognition in older individuals [17,20]
Subclinical hearing loss links with steeper cognitive decline [6]	Chronic subjective tinnitus and executive control of attention impairment might not be directly associated [21]
CAPD might be an early marker of MCI and AD [8–11], and cognitive frailty [12]	Hearing loss, but not ARHL with tinnitus, accelerates age-related gray matter declines [22]
Chronic subjective tinnitus links with MCI [19] and poorer performance in multiple cognitive domains [13–15]	AD hallmarks are not present in the cochlea and cochlear nucleus [31]
ARHL with tinnitus links with MCI [16–18]	Genetic risk for peripheral hearing impairment does not affect cognition [77]
The presence of tinnitus might improve cognitive performance in non-Hispanic patients with hearing loss [20]	Genetic risk for AD does not affect peripheral hearing [77]
AD and its preclinical stages link with CAPD [25–28]	
Semantic dementia links with tinnitus and hyperacusis [29]	
Parkinson's disease and dementia with Lewy bodies link with auditory hallucination [30]	
AD hallmarks are also present also in the central auditory pathway and auditory related cortical areas [31]	
Midlife hearing loss links with volume decline in the entorhinal cortex and hippocampus [37]	
Hearing restorative devices slow the decline of cognitive performance in the short- and long-term period [51]	
Cognitive impairment counteracts the gain of the usage of hearing aids by participants with hearing loss [53]	
Genetic risks for AD [77] and peripheral hearing impairment [78] affect central auditory function	

ARHL, age-related hearing loss; AD, Alzheimer's disease; CAPD, central auditory processing disorder; MCI, mild cognitive impairment.

tural constructs of the auditory system and brain are determined by endogenous environmental factors, such as genetic factors. The extrinsic constructs, or auditory and cognitive reserves, are determined by exogenous environmental factors, including stresses and EE experiences. As mentioned, environmental stresses could accelerate the decline of auditory and cognitive reserves [70]. In contrast, EEs, such as auditory-based therapeutic interventions (e.g., music training or bilingual learning), can increase auditory and cognitive reserves and performance [71]. The consequence is that older individuals with better auditory and cognitive function might be accompanied by more severe neuropathological changes due to greater functional reserves. In addition, it is little known whether non-auditory EEs, including more educational, occupational, or physical activity, also improve auditory reserve and function since these EEs can increase the cognitive reserve and improve cognitive function, as well as diminish age-related structural changes in the brain, and reduce the risk of cognitive impairment [61]. In sum, the effects of environmental factors significantly increase the difficulty of explaining the causal relationship between ARHL with tinnitus and cognitive performance.

3.3 The Detection of Peripheral and Central Hearing Loss

Pure-tone audiometry (PTA), a gold standard for testing hearing loss, is generally used to assess peripheral (cochlea and auditory nerve) function. In fact, PTA thresholds are not only affected by cognitive performance, including executive function, attention, and brainstem pathologies [72,73] but also do not fully reflect central auditory processing ability [74]. Furthermore, audiograms in cognitive-decline subjects may not always reflect their hearing ability. Among cognitive-decline individuals, such as those with AD and its prodromal stages, CAPD may be captured by

questionnaires, CAPD test batteries, or evoked response assessment [26,75]. However, those patients had normal or near-normal peripheral hearing as measured by PTA. However, conditions in which AD patients with cochlear synaptopathy due to hidden hearing loss that preserve PTA values but who have abnormal speech-in-noise performance could not be excluded. An ideal study population on which to investigate the effect of early hearing loss on cognition, using non-auditory testing instruments, would be those prelingually deaf signers who live in a signing environment. They have auditory deprivation but without concomitant social deprivation [34,76].

4. Recommendation on the Interrelationship between Age-Related Hearing Loss, Tinnitus, and Cognitive Impairment

The anatomical and functional connectivity of the central auditory system, limbic system, and MTL is the early critical setting of interaction. A few novel studies attempted to elucidate the causal relationship. One study tested the hypothesis that shared genetics or incipient AD may influence hearing status in older adults without dementia by using data established at birth with genetic variation in AD risk and whether hearing impairment may influence cognition, by using data with genetic variation in hearing impairment risk, indicated that genetic risk for AD also influences central auditory function. However, the test failed to find evidence that genetic risk for hearing impairment affects cognition [77]. Nevertheless, the genetic risks for peripheral deafness (e.g., congenital, prelingual, postlingual, and ARHL) can result in central auditory deficits [78]. Together with the aforementioned evidence (Table 1, Ref. [2–4,6–22,26–31,37,51,53,77,78]), we propose that the central hearing system might be the common target of neurodegenerative diseases and peripheral hearing loss and/or tinnitus. This suggests an integrated mechanism that contains a directional interaction between the peripheral and central auditory systems, the auditory system and the cognitive brain.

Although the chronological sequence of ARHL with tinnitus is much more frequently observed than the sequence of cognitive decline with posterior hearing loss, A double “hit” hyperthesis can explain the bidirectional relation. On the one hand, a hit might be multiple common factors, such as aging, vascular impairment, inflammation, and lifestyles, and might result in multi-system vulnerability and auditory and cognitive impairment. The “abuse” of cognitive resources for listening can further cause the depletion of the brain and cognitive reserves. The same argument could be used for the “abuse” of visual information (reading or visual tasks) to exhaust cognition. The level of education is associated with a delayed cognitive impairment; intellectual exercises that require visual input and processing are commonly used to slow the progression of MCI. On the other hand, brain vulnerability due to cognitive impairment and dementia might be a hit resulting in the reserve decline of the auditory brain and CAPD, which affect peripheral tinnitus via the auditory efferent system. However, peripheral auditory impairment also might be a hit causing the decline of auditory cognition by the cochlear afferent system, indirectly causing global cognitive depletion.

5. Conclusions

The evidence for the bidirectional relationship between ARHL and/or tinnitus and cognitive performance is not conclusive. We propose that auditory cognitive impairment in the central auditory system is the common target of peripheral auditory impairment and dementia or its precursor. Auditory cognition might be an early diagnostic signal of incipient dementia. Hearing restoration, together with sustained multimodal EE, combining motor, cognitive, sensory, and social stimulation, accompanying modifiable lifestyles, should be preferable to the implementation of single-domain training and should have far-researching benefits for auditory and cognitive performance.

Author Contributions

QR, BC, and FP designed the research study, conceptualized and conducted a literature review. QR and FP wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest. Qingwei Ruan, Bing Chen, and Francesco Panza are serving as the Guest editors of this journal. We declare that Qingwei Ruan, Bing Chen, and Francesco Panza had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Gernot Riedel.

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