



## The Link between Hidden Hearing Loss and Cognitive Decline

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### Abstract

Sensorineural Hearing Loss (SNHL) is a common corollary of ageing and can also occur adventitiously, such as with exposure to noise or ototoxic drugs. The underlying pathology of SNHL is an extensive loss of sensory hair cells in the cochlea, but SNHL may also arise from early neural degeneration and cochlear synaptopathy often not detected by conventional pure tone audiometry. This form of hearing loss, described as “hidden hearing loss”, provides some explanation for the hearing difficulties reported despite normal or near-normal auditory thresholds. SNHL not only impairs communication and social interactions, but emerging evidence from animal and clinical studies suggests that SNHL also contributes to cognitive decline. This review will discuss the mechanisms underlying hidden hearing loss, followed by a review of the literature investigating the correlation between hearing deficits and cognitive decline.

**Keywords:** Sensorineural hearing loss; Hidden hearing loss; Cochlear synaptopathy; Cognitive decline

### Sensorineural Hearing Loss

Sensori Neural Hearing Loss (SNHL) is characterized by the loss of sensory hair cells and subsequent neural degeneration in the cochlea. The sensorineural tissues of the cochlea have no regenerative capabilities, thus rendering cochlear damage irreversible. The survival of afferent Spiral Ganglion Neurons (SGN) in the cochlea is influenced by neurotrophic factors (BDNF, NT-3) released from hair cells and supporting cells in the cochlear sensory epithelium [1]. This neurotrophic support is lost when hair cells die, resulting in retraction of afferent SGN dendrites and secondary loss of SGN. However, recent studies suggest that SGN loss can occur independent of hair cell death, and extensive loss of the auditory afferent synapses, rather than hair cell death, is the earliest sign of cochlear damage [2-8]. The primary loss of afferent nerve synapses due to noise or aging has been named “cochlear synaptopathy” or “cochlear neuropathy”. This is not obvious as a change in auditory threshold as shown in a pure tone audiogram, but it probably leads to difficulties in speech discrimination in noisy conditions and central auditory deficits that can explain at least some of the declining auditory performance in aging individuals with normal audiograms (also known as “hidden hearing loss” or HHL) [5-9].

### Cochlear Synaptopathy

Cochlear synaptopathy and loss of afferent neurons caused by excessive release of glutamate is a widely-accepted mechanism for neural degeneration in Noise-Induced Hearing Loss (NIHL). Swelling of afferent synaptic terminals at the inner hair cell-auditory nerve synapse (type I synapse) has been observed immediately after noise exposure in experimental animal models [10]. Swelling of type I synapses is associated with both temporary and permanent auditory threshold shifts and is closely followed by neural degeneration [2,3]. Pure tone audiometry and Auditory Brainstem Responses (ABR) threshold measures are relatively insensitive to diffuse neural injury; hence the recovery of hearing thresholds is not always indicative of full neural recovery [8]. Cochlear imaging methods, such as confocal microscopy, have been used to quantify the extent of neural loss, which reveal intact hair cells but significant loss of pre-synaptic ribbons that persist for up to 2 years after noise exposure [3]. It was suggested that chronic noise exposure leads to glutamate excitotoxicity, subsequent retraction of synaptic terminals and suppression of the neurotrophin cascade essential for neural survival [3]. Glutamate release is clearly implicated in the synaptic injury, although non-glutamate mechanisms may also be involved [11]. Excessive glutamate release triggers a large influx of calcium, potassium and sodium ions into the SGN, resulting in an osmotic imbalance, synaptic terminal swelling and disruption [11]. Both L- and T-type calcium channels are implicated in this

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process, where an increase in permeability for calcium ions triggers further release of intracellular calcium ions. Calcium overload initiates a vicious cycle of more glutamate release and activation of downstream cell death pathways [12,13].

## Low Spontaneous Rate Fibres as a Target for Synaptopathy

Auditory Nerve Fibres (ANF) with low Spontaneous Discharge Rates (SR) appear to be the main target of noise-induced synaptopathy. This explains the abnormal suprathreshold ABR amplitudes observed despite near normal ABR and auditory thresholds in animals [14]. Although the reason for this preference of the low SR fibres is not yet proven, it may be due to metabolic differences and glutamate recycling in these fibres. Low SR ANF has lower numbers of mitochondria, related to a lower metabolic demand compared to high SR fibres. Mitochondria act as a buffer against intracellular calcium overload during excitotoxic damage, and the lower numbers of mitochondria thus may lead to poorer resistance to calcium-induced damage [14]. Secondly, low SR fibres express fewer Glutamate Aspartate Transporters (GLAST), which are essential for the re-uptake of glutamate after an acoustic injury [9] and thus there may be higher levels of glutamate in the synaptic cleft after noise exposure. Hidden hearing loss represents hearing difficulties despite normal or near normal thresholds, most likely because low SR fibres are not associated with detection of low level pure tones, but contribute to detection of higher level sounds and are essential for decoding of complex sound stimuli in a noisy environment as they contribute to detection of a wider dynamic range [8,9]. Therefore, selective damage to these fibres likely induces deficits in the coding of complex signals, thus affecting speech intelligibility.

## Current Treatments for Hidden Hearing Loss

Although there is increasing evidence that HHL occurs in humans, there is still no clear diagnostic tool and hence currently no effective treatment. Individuals with suspected HHL are not usually fitted with hearing aids since it only amplifies acoustic signals and cannot improve intelligibility of speech. Previous animal studies have attempted to reduce the extent of synaptic damage by restoring neurotrophic factors to promote reconnection between hair cells and nerve fibres [15-17]. These studies have shown that neurotrophin-3 was more important for the survival of SGN while BDNF is responsible for the survival of vestibular neurons [15]. SGN degeneration reduces the number of functional synapses, and NT-3/TrkC signaling is down-regulated resulting in a vicious cycle of further neural degeneration. In another study, delivery of NT-3 and BDNF improved the number of afferent auditory synapses almost to the level of the normal hearing ear and extended the survival of SGNs [16]. Similarly, synaptogenesis of auditory synapses and axonal regrowth has been demonstrated in cochlear explants treated with BDNF and NT-3 after excitotoxic injury, which further emphasizes the need for neurotrophic support in maintenance of neural structures [17]. The understanding of the mechanisms has led to effective experimental strategies to reduce the synaptic changes in animals but this has yet to be translated to humans due to the lack of an effective diagnostic tool.

## Hearing Loss and Cognitive Decline

Cognition is defined by the “mental action or process of acquiring knowledge and understanding through thought, experience, and the senses” (English Oxford Dictionaries). Cognition comprises various

domains including sensory and motor processing, attention, executive function, and memory. Cognitive decline describes a spectrum of conditions ranging from mild cognitive impairment to full dementia [18]. Many risk factors have been described for the development of age-related cognitive decline, but the hearing loss in midlife ranks highest amongst the potentially modifiable risk factors for dementia in developed countries [19,20]. Other common risk factors include hypertension, obesity, smoking, depression, physical inactivity, social isolation and diabetes [20], but the balance of risk factors may be different in developing countries [21]. Noise induced-SNHL manifests in the form of sensory hair cell damage, neuronal degeneration, and altered frequency responses along the ascending auditory pathway. However, much of the focus has shifted to study the effect of noise on non-classical auditory pathways that involve structures responsible for learning and memory, such as the hippocampus. Findings from animal studies show extensive damage of the cellular networks in the hippocampus, consistent with impaired spatial abilities in functional studies. The remaining sections will review findings from these studies, as well as clinical observations on human participants with hearing loss.

## Hypotheses of Cognitive Decline

Several hypotheses have been put forward to explain the link between hearing loss and cognitive decline [22,23]. The information degradation hypothesis suggests that hearing loss causes cognitive decline [22]. Effortful listening increases compensatory mental effort to improve perception by depleting limited cognitive resources, thus compromising other cognitive processes (e.g. working memory, attention). This hypothesis implies that the restoration of auditory input will reduce effortful listening, and thus reduce cognitive load and improve cognitive performance. In contrast, the sensory-deprivation hypothesis describes permanent cognitive decline from neuropathological changes such as deafferentation and reorganization of cortical areas due to reduced auditory stimulation. In addition, the relationship between hearing loss and cognitive decline may also be influenced by social isolation. For example, in one study, after adjusting for factors such as depression and social networking, the difference in the rate of cognitive decline between those with self-reported hearing loss and normal hearing participants did not differ [24]. Lastly, the common cause hypothesis states that hearing loss and cognitive decline results from age-related degenerative changes shared between the auditory and cognitive systems. Common factors might include vascular insufficiency, oxidative stress, inflammatory responses and genetics [23].

## Animal Studies

Various animal models have been used to assess the behavioral and neuropathological changes caused by hearing loss that may be associated with cognitive changes [25-30]. Disruption of hippocampal neurogenesis was demonstrated by a reduction in the number of neuronal precursor and proliferating cells in the hippocampus of rats with hearing loss [25]. NIHL also significantly reduced the stimulating effect of learning on various stages of neurogenesis in the mouse hippocampus [26]. In addition, the complexity of the dendritic trees and the total projection length of each neuron are also reduced in the hippocampus of the animals with hearing loss compared with the normal hearing group [26]. Moderate noise exposure can progressively impair the learning and memory ability of mice, probably due to oxidative cellular damage in auditory pathways, tau hyperphosphorylation in the hippocampus, and faulty

auditory coding particularly in the inferior colliculus [28]. One of the mechanisms underlying the disruption of the hippocampal network is noise-induced oxidative damage along the lemniscal pathway leading to the hippocampus. The peroxidation levels in the Auditory Cortex (AC), Inferior Colliculus (IC) and hippocampus were assessed by measuring the malondialdehyde (MDA) content and Superoxide Dismutase (SOD) activity 6 weeks after moderate noise exposure [28]. The results demonstrated greatest peroxidative damage in the hippocampus, compared to that observed in the AC and IC [28]. Increased phosphorylation of tau proteins in the hippocampus was probably also a consequence of peroxidative damage.

Impulse noise may also result in a temporary decrease in cognitive function as evidenced by poor spatial memory in the Morris Water Maze (MWM) associated with aberrant tau hyperphosphorylation in the hippocampus [29]. This was consistent with other studies that also demonstrated spatial memory deficits after exposure to traumatic noise [26-28]. In another study, the effect of NIHL during early development and its long-term impact on cognitive function was investigated in mice [26]. The study demonstrated a strong correlation between elevated auditory thresholds and poor performance in MWM. Findings from these studies provide clear evidence for association between NIHL and cognitive deficits. However, the cause and effect relationship between the two is still unclear. More direct evidence that hearing loss is indeed causing cognitive decline was provided by Park and colleagues [30]. In that study, C57BL/6 mice exposed to traumatic noise showed elevated Auditory Brainstem Response (ABR) thresholds and poorer performances in spatial working and recognition memory tasks than the controls. This was associated with p-tau and lipofuscin accumulation in the hippocampus. Working memory impairment was reversible, whereas recognition memory impairment was permanent. This study thus provides behavioral and histopathological evidence for hearing-related cognitive decline [30].

## Clinical Observations

In contrast to the animal studies, clinical studies have presented compelling evidence for the association between hearing loss and cognitive decline [31-39]. Participants from the Baltimore Longitudinal Study of Aging (BLSA) with greater degree of hearing loss demonstrated poorer performance on measures of global cognitive function (mini mental state examination, MMSE), memory and executive function (Stroop test, free recall test, and trail making tasks) [31]. These findings were consistent with the cognitive load hypothesis, where central compensatory recruitment of cognitive resources takes place to improve auditory perception at the expense of other cognitive processes [31]. In another longitudinal study, elderly participants were followed up over a decade to determine whether hearing loss at baseline (beginning of study) accelerated cognitive decline and development of dementia [19]. The findings showed that 16.3% of the participants with baseline hearing loss developed dementia compared to 12.1% of those without baseline hearing loss. Furthermore, the authors reported mean time to dementia was shorter in the hearing loss group compared to those with normal hearing. After controlling for additional factors such as gender, cardiovascular risks, and presence of the APOE-e4 allele; hearing loss was shown to be an independent variable associated with accelerated rates of cognitive decline and development of dementia [19]. Moreover, a longitudinal study and meta-analysis reported men with hearing loss were 69% more likely to develop dementia over 11 years than those with near normal hearing [32]. Similarly, Armstrong and colleagues

[33] found that hearing loss at the beginning of a two-year study was associated with poorer scores of verbal recall and digit span forward. The association between cognitive performances with changes in hearing status was also assessed and found no reverse causation between the two, suggesting hearing loss as a risk for cognitive decline [33]. Another study [34] found that the effect of hearing loss was specific to certain cognitive domains, namely factual knowledge and logical reasoning, attention and working memory. The hearing-impaired group did not demonstrate the same resistance to decline in these domains as observed in those with normal hearing. This study suggests that fluid cognitive processes such as working memory are more vulnerable to the aging effect, and this is likely exacerbated with the presence of a hearing impairment [34].

Evidence for an association between hidden hearing loss and cognition is currently very limited. A study by Delano and colleagues [35] used suprathreshold auditory brainstem responses (ratio of wave I and V) as an index of cochlear neuropathy and found that the reduction in ABR threshold was correlated with MMSE scores in healthy elderly adults with normal/near normal pure tone detection thresholds [35]. However, there are studies that show no change in suprathreshold ABR in people with speech-in-noise difficulties and there are some concerns about validity of MMSE with people who may not have good hearing and may take time to process the information because of their hearing loss. Therefore, HHL may be useful as an early indicator for future cognitive decline and to guide implementation of early interventions, but there is currently no established protocol for the diagnosis of HHL. Further research is needed to establish a diagnostic measure of HHL; the ratio between Compound Action Potential (CAP) and Summating Potential (SP) looks most promising to date.

In addition to the clinical observations, brain imaging studies have also contributed to understanding of the association between hearing loss and cognitive decline. Individuals with hearing impairment demonstrated greater reduction of grey matter in the frontal cortex, superior and medial frontal gyri, in addition to disrupted white matter tracts leading to central auditory processing areas in the right hemisphere [36]. The affected areas are responsible for cognitive function, attention, as opposed to sensory processing. However, this study lacked cognitive tests to confirm whether damage in these areas corresponds to functional cognitive decline. In another study, accelerated brain atrophy was observed along with greater reduction of temporal lobe grey matter in those with hearing impairment compared to the normal hearing counterparts [37]. More specifically, greater volume decline was found in the superior, medial and inferior temporal gyrus, and in the parahippocampal gyrus in the right hemisphere consistent with the changes reported by Husain and colleagues [36]. It was suggested that these findings possibly reflect the common cause hypothesis, as shared neuropathologic processes contribute to parallel decline of the auditory and cognitive function [37].

According to the information degradation hypothesis, loss of auditory input depletes limited cognitive resources to improve perception and impair other cognitive processes. There are some studies reporting better cognitive performance in hearing impaired individuals wearing hearing aids [24,38,39] although the evidence overall is not consistent and controlled trials are needed [40]. However, it is important to note that the variability observed from subjects in observational studies is influenced by factors that cannot

be controlled for [41]. This includes the years of hearing aid use, adequacy of hearing aid fit, the number of hours worn per day, all of which will influence the success of the intervention [39]. Several randomized controlled trials are underway to address the issue of hearing interventions on cognitive decline. An ongoing study by Deal et al. [42] investigates the efficacy of aural rehabilitation in reducing cognitive decline in older adults in a randomized control trial. Based on a successful feasibility study [43], participants are randomly allocated to receive best-practice hearing intervention and fitted with hearing aids or assigned to the successful aging health education group. The primary outcome measures include global cognitive function accessed via a battery of neuropsychological tests representing various cognitive domains, incident dementia, neuroanatomical changes, and various psychoenvironmental factors. The findings from this study will become available in 2022, which will reveal the long-term effect of hearing loss treatment on cognitive function [42]. A further trial of sensory intervention (hearing, vision or both) is also planned [44].

## Conclusion

Evidence from animal and clinical studies suggests that hearing loss is an important modifiable risk factor for cognitive decline. The underlying mechanisms of cognitive decline as a result of auditory deficits are yet to be elucidated. Further research will reveal whether the correction of auditory deficits can indeed delay the progression of cognitive decline.

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