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Hidden hearing loss: Fifteen years at a glance

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A B S T R A C T

Hearing loss affects approximately 18% of the population worldwide. Hearing difficulties in noisy environments without accompanying audiometric threshold shifts likely affect an even larger percentage of the global population. One of the potential causes of hidden hearing loss is cochlear synaptopathy, the loss of synapses between inner hair cells (IHC) and auditory nerve fibers (ANF). These synapses are the most vulnerable structures in the cochlea to noise exposure or aging. The loss of synapses causes auditory deafferentation, i.e., the loss of auditory afferent information, whose downstream effect is the loss of information that is sent to higher-order auditory processing stages. Understanding the physiological and perceptual effects of this early auditory deafferentation might inform interventions to prevent later, more severe hearing loss.

In the past decade, a large body of work has been devoted to better understand hidden hearing loss, including the causes of hidden hearing loss, their corresponding impact on the auditory pathway, and the use of auditory physiological measures for clinical diagnosis of auditory deafferentation. This review synthesizes the findings from studies in humans and animals to answer some of the key questions in the field, and it points to gaps in knowledge that warrant more investigation. Specifically, recent studies suggest that some electrophysiological measures have the potential to function as indicators of hidden hearing loss in humans, but more research is needed for these measures to be included as part of a clinical test battery.

1. What is hidden hearing loss?

1.1. Hearing Loss

The gold standard for diagnosing hearing loss in the clinic is audiometry. Audiometry determines the softest audible stimulus, such as a pure tone, warble tone or narrow-band noise, in quiet as a function of frequency (typically between 125 and 8000 Hz). The intensity of this sound at the detection level is referred to as the 'hearing threshold'. This threshold is compared to a reference threshold, which is established as the expected median threshold for an 18-year-old individual of the same gender, as defined by International Organization for Standardization (2017). If the hearing threshold is less than 25 dB above the reference threshold at that frequency, it is considered to be within the normal hearing range; if it is 25 dB or more above the reference threshold, it is considered to indicate clinical hearing loss. Note that based on this definition, a wide range of audiometry thresholds fall within the normal hearing range. The types of hearing loss and their causes vary. 'Conductive' hearing loss blocks sounds from reaching the inner ear and is generally caused by any kind of obstruction in the outer ear or middle ear, as well as some other structural abnormalities (e.g., eardrum perforation). It can often be reversed. 'Sensorineural' hearing loss is permanent, describes neural deficits in the inner ear and/or auditory pathway, and is typically caused by certain genes, aging, or noise exposure (Smith et al., 2005). Of those, aging and noise exposure are the most common causes of acquired sensorineural hearing loss (Tanna et al., 2024).

1.2. Hidden hearing loss

About 1–10% of patients undergoing testing in the audiology clinic report having hearing difficulties but have clinically normal audiometric thresholds (Zhao and Stephens, 2007). These patients often describe their hearing difficulties, particularly in noisy environments, with phrases like "I can hear, but not understand" (Lopez-Poveda, 2014; Zeng, 2000). This perceptual anomaly is often referred to as hidden hearing loss (HHL), reflecting the combination of hearing difficulties in the absence of clinically abnormal audiometric thresholds (Liberman and Kujawa, 2014). While the term HHL may have some ambiguity in the literature, in this review, we define HHL as perceptual difficulties in hearing that cannot explained by audiometric results. HHL can potentially stem from various underlying causes. The exact physiological causes of HHL remain unknown in humans. Nevertheless, recent studies in animals have suggested that symptoms resembling HHL may result from auditory deafferentation. Auditory deafferentation is the loss of early afferent signals, such as the loss of inner hair cells (IHC) or the loss

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of synapses between IHC and auditory nerve fibers (ANF). Importantly, these studies have shown that auditory deafferentation-related deficits in both physiological and behavioral measures of auditory function are not necessarily accompanied by a detectable deficit in audiometric threshold (Chambers et al., 2016; Kujawa and Liberman, 2009; Lobarinas et al., 2016; Resnik and Polley, 2021; Sergeyenko et al., 2013; Wu et al., 2019).

2. Why does hidden hearing loss matter?

2.1. Hearing loss matters

Hearing loss is a serious concern in healthcare due to its high prevalence and its impact on a person's quality of life. It is estimated that hearing loss affects about 18% of the population worldwide (Wilson et al., 2019). There are well over one billion cases of mild to profound hearing loss, and in almost half of these cases patients complain of disabling effects on their lives due to their hearing difficulties (Wilson et al., 2019). Hearing loss is most prevalent in the elderly, with over 40% of individuals aged 60–69 suffering from a hearing impairment (Hoffman et al., 2017) and over half for those aged over 70 (World Health Organization, 2018). Importantly, while hearing loss itself is a sensory deficit, its impacts go well beyond the sensory domain, extending to mental well-being, cognitive functions, and an elevated risk of dementia (Liang et al., 2021; Thomson et al., 2017). Moreover, hearing loss also creates stigma (Hétu and Getty, 1996), threatens identity (Gagné et al., 2009; Southall et al., 2010), reduces self-esteem (Lash and Helme, 2020), and induces a feeling of loneliness (Ellis et al., 2021; Shukla et al., 2020).

2.2. Hidden hearing loss matters

IHC-ANF synapses are typically the first cochlear structures to be affected by aging or noise exposure, and these synapses are lost at a faster rate than outer hair cells (OHC) or IHCs (Sergeyenko et al., 2013; Wu et al., 2019). This suggests that HHL could appear before the development of clinically abnormal auditory thresholds, in which case HHL might be regarded as a natural process in normal aging (Wu et al., 2019). Although the impact of HHL is not as severe as that of clinical hearing loss, HHL also affects communication in daily life, as conversations in the real world usually occur in noisy environments. It is conceivable that such hearing difficulties in noise affect cognitive functions (Moore et al., 2014).

Hidden hearing loss might also predict later clinical hearing loss. With aging, the loss of IHC-ANF synapses is faster than the loss of OHCs (Wu et al., 2019, 2020), and IHC-ANF loss could impair the functioning of nearby surviving IHC-ANF synapses (Bullen et al., 2019). HHL is thought to emerge as IHC-ANF synapses are lost, and HHL would consequently be expected to emerge earlier than clinical hearing loss (which typically involves the loss of OHCs). As such, HHL could be used to predict later, more severe hearing loss, which would make early intervention possible. However, while this hypothesis is tempting, it is currently only supported via a correlational association between inner and outer hair cell loss and IHC-ANF synapse loss (Wu et al., 2020), and to date there is no solid evidence in humans that suggests that people with HHL are more likely to develop clinical hearing loss later in life (see the recent review in Trevino and Lobarinas 2021).

From a systems point of view, researchers can operationalize the loss of IHC-ANF synapses as an experimental tool to probe its effects on the auditory system and its perceptual consequences. The precise degree of auditory deafferentation can only be quantified *post mortem* in humans or animals. If available, these measurements can then be correlated with physiological or behavioral data collected at an earlier stage. However, as we will discuss in Section 3.2, researchers can induce controlled degrees of auditory deafferentation in animals, which allows a more detailed and causal investigation of central adaptation to reduced or degraded peripheral inputs. As we will discuss in more detail in Section 4, such adaptations include central gain, unchanged or enhanced central response after peripheral loss (Chambers et al., 2016; Harris et al., 2022; Schaette and McAlpine, 2011), and internal noise, hypersynchronized neural activity in the central auditory system after peripheral loss (Resnik and Polley, 2021). These maladaptive central changes may also help explain tinnitus and hyperacusis (Auerbach et al., 2014; Plack et al., 2014).

3. What causes hidden hearing loss?

3.1. Innervation of auditory nerve fibers in the cochlea

The cochlea is a bony structure that houses the hair cells and the synapses between hair cells and ANFs. The human cochlea has around 3500 IHCs, 12,000 OHCs, and a total of about 31,000 ANFs (Nadol, 1988). IHCs encode the location of displacement on the basilar membrane by releasing neurotransmitters. When the neurotransmitters surpass a threshold that is sufficient to depolarize the postsynaptic ANFs, the ANFs generate an action potential which is then passed along their axon to the cochlear nucleus (Pickles, 2013). OHCs both amplify and sharpen the displacement of the basilar membrane (Ashmore, 2008). Both IHCs and OHCs are innervated by ANFs, albeit by two different types of ANFs: Type I and Type II ANFs. Some of the characteristics of Type I and Type II ANFs are listed in Table 1. For a more detailed review of the anatomy of hair cells and ANFs, see Carricondo and Romero-Gómez (2019) and Eybalin (1993). Note that some ANF characteristics vary between species (see Nayagam et al. 2011 for a detailed comparison of ANFs between species). Humans have very different ANF characteristics, and we will discuss human ANFs in detail later in this section.

Since degradation of IHC-ANF synapses is a likely etiology of HHL (Kujawa and Liberman, 2009), we will focus on Type I ANFs. Type I ANFs can be further divided into three groups according to their intrinsic spontaneous rate (SR) of firing action potentials: low-SR, medium-SR, and high-SR ANFs (Liberman, 1978). In cats, low-SR, medium-SR, and high-SR fibers make up approximately 15%, 25%, and 60% of Type I ANFs, and have high, medium, and low thresholds to sound, respectively (Liberman, 1978). The SR-subgroups can also be differentiated via other response characteristics, such as their rate-level functions (shown in Fig. 1 in gerbils), tuning curves, and more subtle aspects of their peristimulus time histograms (PSTHs) (Huet et al., 2016; Liberman, 1978). Furthermore, these SR-subgroups of Type I ANFs differentiate in terms of mRNA expression (Shrestha et al., 2018), vulnerability to noise (Furman et al., 2013) and potential for recovery (Suthakar and Liberman, 2021), and vulnerability to ototoxic drug treatment (Bourien et al., 2014). The SR-specific vulnerability to noise and their recovery are different across species, where CBA/CaJ mice show irreversible loss of all SR types, while in guinea pigs such loss seems to be specific to low-SR ANFs, which subsequently recover (Furman et al., 2013; Hickman et al., 2020; Song et al., 2016; Suthakar and Liberman, 2021). The exact function of these ANF SR-subgroups for sound encoding remains unclear. A considerable body of research (for example, Bharadwaj et al. 2014, Paul et al., 2017a) suggests that low-SR fibers play an important role in encoding suprathreshold sounds, which can be partly attributed to their comparatively wide dynamic range

Table 1
Characteristics of ANF subtypes.

	Type I ANF	Type II ANF
Innervated hair cells	IHC	OHC
Innervation	10–20 ANFs to one IHC	One ANF to about 15–20 OHCs
Proportion	90–95% of all ANFs	5–10% of all ANFs
Fiber characteristics	myelinated	unmyelinated
	large diameter	small diameter
	bipolar	pseudounipolar
	fast conduction velocity	slow conduction velocity

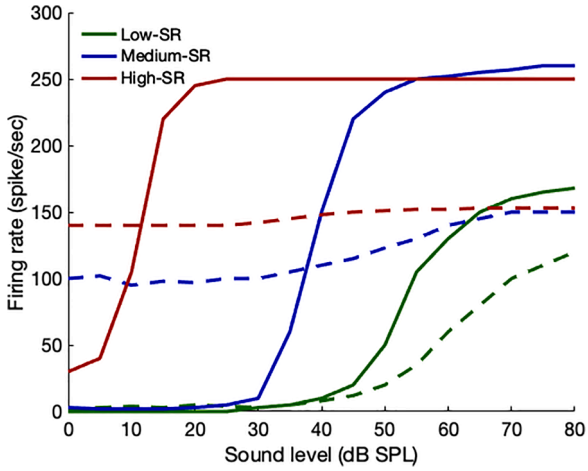

Fig. 1. Schematic of the average rate-level function of the low-, medium-, and high-SR gerbil Type I ANFs in 60 dB SPL noise (dashed traces) and in silence (solid traces). (Data from Huet et al. 2016)

above ~30 dB SPL (as illustrated in Fig. 1). However, it has been suggested that rather than the simple aggregate of firing rate, it might instead be the fluctuation profile of ANF responses across time and frequency that encodes complex information about the incoming sound, especially for speech (Carney, 2018). The fluctuation profile of low- and medium-SR ANFs might also be a major driver of cochlear efferents, such as the medial olivocochlear (MOC) system (Carney, 2018).

Translating what we know about animal auditory nerve fibers (ANFs) to humans presents several challenges. First, most of the ANF characteristics mentioned so far are derived from studies that were conducted on small mammals, but some ANF characteristics can differ substantially between humans and animals. For instance, more than 90% of Type I ANFs and approximately half of Type II ANFs are unmyelinated in humans, while in small mammals type I ANFs are myelinated and type II ANFs are unmyelinated (Nayagam et al., 2011; Ota and Kimura, 1980). Second, human ANFs seem to also form synaptic connections with other ANFs, which has not been shown in small mammals (Kimura et al., 1979). Third, it is worth noting that the conventional assumption that low-SR ANFs have high thresholds and high-SR fibers have low thresholds does not hold true in non-human primates, where all Type I ANFs were found to have a similar distribution of thresholds (Joris et al., 2011). Fourth, our understanding of how human ANFs should be grouped based on their spontaneous firing rate (SR), as well as their relative proportions, remains limited. The substantial disparities between human ANFs and those in small mammals raise significant questions about the applicability of animal research results on ANF loss to humans.

3.2. Main causes of auditory deafferentation

3.2.1. Drug-induced auditory deafferentation

Some potential causes of auditory deafferentation include aging, noise exposure, and ototoxic drugs. Since ototoxic drugs can be used to target specific structures in the inner ear, they are widely used in rodent studies to induce auditory deafferentation (Lee et al., 2019; Yuan et al., 2014). This enables the study of the effects of auditory deafferentation in isolation, without accompanying OHC loss.

The most widely used ototoxic drug in rodent auditory studies is ouabain. Its targets are Type I spiral ganglion neurons (SGNs), while sparing IHCs, OHCs and Type II SGNs (Yuan et al., 2014). Ouabain affects Type I SGNs equivalently across frequencies (Yuan et al., 2014). Studies using ouabain to impair the SGNs show that the resulting auditory deafferentation does not induce changes in behavioral audiometry measures, even if the loss reaches 95% (Chambers et al., 2016). However, with this level of auditory deafferentation, the behavioral tone detection threshold in noise is increased by about 20 dB, suggesting that ouabain treatment might be a viable approach to induce the behavioral symptoms typical of HHL.

Whereas ouabain is widely used in rodents, kainic acid (KA), which also introduces dysfunction of IHC-ANF synapses, is predominantly used in avian species. The results are similar to those of ouabain in mice in the sense that after KA application, the action potentials conveyed by IHC-ANF synapses are blocked (Lee et al., 2019; Ruel et al., 2000), without a behavioral threshold shift in silence or evidence of dysfunction of OHCs (Wong et al., 2019). Budgerigars with 40%–70% ANF loss showed no tone detection deficits in noise (Henry and Abrams, 2021).

As we will mention in 3.2.2 and 3.2.3, IHCs are less likely to be affected by aging or noise exposure than IHC-ANF synapses. However, the loss of IHCs should theoretically have similar effects on perception as the loss of IHC-ANF synapses, since they both result in auditory deafferentation (Sergeyenko et al., 2013; Valero et al., 2017; Wu et al., 2019). Carboplatin, a neurotoxin, has been shown to cause IHC-specific loss: carboplatin treatment in chinchillas leads to a loss of 55–95% of IHCs across all frequencies, without any loss of OHCs (Lobarinas et al., 2016). Perhaps somewhat surprisingly, this loss of IHCs did not lead to a significant behavioral threshold shift in quiet (Lobarinas et al., 2016). This is similar to the results reported in Resnik and Polley (2021), where a loss of ~70% of SGNs did not affect behavioral thresholds in quiet. However, studies that have used carboplatin to induce IHC-specific loss, did not investigate auditory perception in noise (Lobarinas et al., 2016; Qiu et al., 2000), leaving its potential relation to HHL uncertain.

Even though ototoxic drugs offer a well-controlled method to study auditory deafferentation in animals, their scope is arguably somewhat limited, since auditory deafferentation in more natural scenarios (e.g., due to aging or noise exposure) may not impact all frequencies equally and may be accompanied by OHC loss.

3.2.2. Age-related auditory deafferentation

With aging, cellular and neural degeneration occurs naturally in the cochlea, including the loss of IHC-ANF synapses, the loss of OHCs, the loss of SGNs, and the degeneration of stria vascularis (Sergeyenko et al., 2013; Tarnowski et al., 1991; Wu et al., 2019, 2020). This age-related neural degeneration is similar in humans and CBA/CaJ mice: Fig. 2 synthesizes human vs. CBA/CaJ mouse hair cell loss and synapse loss with aging, combining data from multiple studies (Parthasarathy and Kujawa, 2018; Sergeyenko et al., 2013; Wu et al., 2019). The pattern of

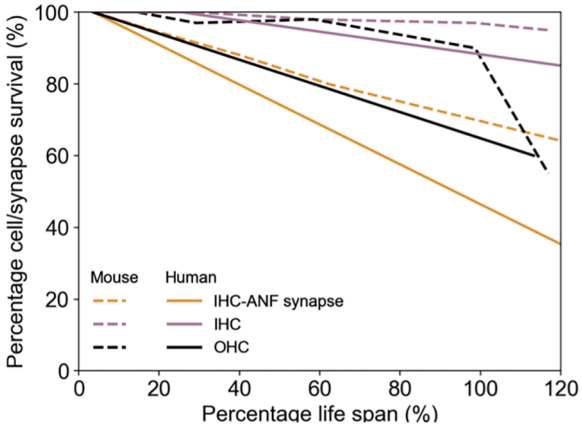

Fig. 2. Comparison of cellular and neural degeneration in humans (solid lines) and CBA/CaJ mice (dashed lines). The x-axis represents the percentage of the typical lifespan (here, 79 years for humans, and 2.1 years for mice (Kujawa and Liberman, 2019)). The y-axis denotes the survival rate of hair cells or synapses. Only the regression lines from Wu et al. (2019) are shown for human data, and the individual data points are omitted. Only the means from Sergeyenko et al. (2013) and Parthasarathy and Kujawa (2018) are displayed for mouse data.

hair cell and synapse loss is similar in both species: the rate of decline is highest in IHC-ANF synapses, followed by that in OHCs, whereas IHCs are the least vulnerable structure. It should be noted that directly comparing the relative loss rate of hair cells is not necessarily straightforward, considering that many other factors could potentially introduce differences across species, for example, the recovery of IHCs and IHC-ANF synapses after degeneration (Chen et al., 2019; Rubel et al., 2013; Song et al., 2016).

Hair cell loss and synapse loss are also frequency specific. In older humans, IHC loss is more severe in the high-frequency range (>8 kHz), while OHCs show a frequency-band specific loss for both high (>8 kHz) and low frequencies (<200 Hz). The IHC-ANF synapse loss is nearly uniform across frequencies, but is slightly more pronounced at high frequencies (Viana et al., 2015; Wu et al., 2019, 2020). Additionally, a multivariable LASSO (Least Absolute Shrinkage and Selection Operator) regression analysis showed that audiometric thresholds in normal aging humans can be predicted well by the degree of IHC, OHC, and IHC-ANF synapse loss, but not by stria atrophy (Wu et al., 2020).

There is some mixed evidence that the different SR subgroups of Type I ANFs might be differentially vulnerable to aging. Shrestha et al. (2018) reported low-SR-specific loss with aging in CBA/CaJ mice, while Heeringa et al. (2020) showed that age-related ANF loss was specific to high-SR fibers in gerbils. It is currently unclear if this change was caused by the specific loss of high-SR fibers or by a shift in the SR of individual fibers (Heeringa et al., 2020). Additionally, data from gerbils suggested a frequency dependency, whereby for high frequencies the loss was specific to low-SR fibers, while for low frequencies the loss was independent of SR group (Lang et al., 2010; Schmiedt et al., 1996).

3.2.3. *Noise-induced auditory deafferentation*

Noise-induced IHC-ANF synapse loss has physiological patterns that are different from those due to aging or ototoxic drugs. The types of noise exposure can vary significantly in duration, intensity, bandwidth, and frequency range. For the scope of the current review, we will focus on the application of a single, high-intensity noise exposure of a certain duration, since this is the most well-studied paradigm in the animal noise-induced auditory deafferentation literature. Based on the impacts of the noise exposure, a single noise exposure can be categorized into one of four severities. From least to most severe, these refer to noise exposure severities that cause (1) no temporary threshold shift (TTS) or IHC-ANF synapse loss; (2) TTS, but no IHC-ANF synapse loss; (3) TTS and IHC-ANF synapse loss; and (4) permanent threshold shift (PTS), IHC-ANF synapse loss and OHC loss (Fernandez et al., 2015; Valero et al., 2017).

In CBA/CaJ mice, applying a single severity level 2 noise exposure (91 dB SPL, 8–16 kHz octave band noise for two hours) led to a TTS of up to 40 dB, which recovered after 2 weeks, at which point no hair cell loss or synapse loss was observable (Fernandez et al., 2015). A severity level 3 noise exposure (93.5–100 dB SPL; 8–16 kHz octave band noise for 2 h) resulted in only slight to moderate IHC-ANF synapse loss at the exposure frequency range. However, most studies have also reported 'off--frequency' effects, where the IHC-ANF synapse loss was 40–50% larger at frequencies above the exposure band (Valero et al., 2018), or throughout the high frequencies (Kujawa and Liberman, 2009). This 'off-frequency' IHC-ANF synapse loss might be due to the expansion of the vibration frequency range of the basilar membrane at high noise exposure levels. There is usually no OHC or IHC loss that accompanies severity level 2 or severity level 3 noise exposure (Fernandez et al., 2015; Kujawa and Liberman, 2009).

Guinea pigs show changes in anatomy following noise exposure that are similar to those observed in CBA/CaJ mice. Severity level 3 noise exposure (106 dB SPL, 4–8 kHz octave band noise for 2 h) resulted in less than 10% IHC-ANF synapse loss in the exposure region, but 20–60% IHC-ANF synapse loss in the frequency band 1–3 octaves above the exposure band. Among all synapses, the low-SR ANF innervated synapses seemed to be affected most (Furman et al., 2013). However, a reanalysis of the data suggested that both low-SR and medium-SR ANF synapses were affected (Marmel et al., 2015). Additionally, a more recent study found that in CBA/CaJ mice all SR-subgroups were equally affected by noise (Suthakar and Liberman, 2021). In contrast to CBA/-CaJ mice, which experience largely irreversible IHC-ANF synapse loss following severity level 3 noise exposure (Kujawa and Liberman, 2009), regeneration of IHC-ANF synapses appears to occur in C57BL/6 mice (Kaur et al., 2019; Kim et al., 2019) and guinea pigs (Hickman et al., 2020; Song et al., 2016). However, the functionality of regenerated guinea pig synapses might not be fully recovered (Song et al., 2016). Taken together, these findings highlight the complexity of noise-induced IHC-ANF synapse loss in animal models.

Non-human primates show similar trends following noise exposure as rodents, with the caveat that non-human primates appear more resistant to noise exposure: a 120 dB SPL 50 Hz narrow-band noise centered at 2 kHz for 4 h only caused a TTS in rhesus macaques (Valero et al., 2017), while this level of noise exposure would result in a PTS in rodents. The TTS was accompanied by a 20–30% IHC-ANF synapse loss near the exposure frequency and very limited IHC or OHC loss. In contrast, the same noise with an intensity level of 140 dB SPL for 4 h or more caused a PTS, which was accompanied by about 80% of synapse loss in combination with severe and moderate levels of OHC and IHC loss, respectively.

A number of studies have investigated correlates of estimated noise induced auditory deafferentation in humans. For ethical reasons, humans cannot be subjected to potentially harmful levels of noise. Instead, the cumulative noise exposure is typically assessed via a questionnaire on self-reported noise exposure history (Beach et al., 2013; Valderrama et al., 2018; Yeend et al., 2017), which suffers from the obvious limitations inherent to subjective self-reports. A common approach in this field is to determine whether the level of self-reported lifetime noise exposure correlates with a particular objective electrophysiological measure (e.g., auditory brainstem response (ABR) wave I). However, the results of such studies have been mixed (Bramhall et al., 2019; Le Prell, 2019; Prendergast et al., 2017a, 2017b, 2019).

An alternative approach has been to identify a group of people with known high occupational or recreational noise exposure. Since occupational and recreational noise exposure vary greatly in terms of intensity and duration, we consider these two types of noise exposure separately. The majority of studies investigating recreational noise exposure did not find evidence for noise induced auditory deafferentation in humans (Fulbright et al., 2017; Grinn et al., 2017; Grose et al., 2017; Prendergast et al., 2017a, 2017b). For occupational noise exposure (such as military service, construction work, and shipyard work), the evidence is stronger (Jiang et al., 2021; Wu et al., 2021), especially in military veterans with a history of firearm usage/exposure (Bramhall et al., 2017, 2021).

It should be pointed out that recreational noise exposure (listed in Beach et al. 2013) might not cause TTS in humans (see Dobie and Humes (2017) for a detailed comparison of neuropathological noise exposure levels across species, including humans). This is in agreement with data comparing rodents and non-human primates, which suggests that non-human primates (and possibly also humans) might be less vulnerable to noise exposure-related synapse loss (Fernandez et al., 2015; Valero et al., 2017). However, whether a similar resilience extends to the ability to regrow IHC-ANF synapses is currently unclear. While there is some evidence that noise-induced IHC-ANF synapse loss might be recovered in guinea pigs and C57BL/6 mice (though not in CBA/CaJ mice) (Song et al., 2016; Suthakar and Liberman, 2021), to date there are no data that would suggest a similar ability in humans.

In conclusion, the impacts of noise exposure vary between species, but at high enough doses noise exposure causes OHC and synapse loss in all mammalian species that have been studied. The complexity of IHC-ANF synapse loss after noise exposure (e.g., the vulnerability to noise, recovery after noise exposure, and the cumulative effect of noise exposure), makes it difficult to transfer findings from animals to humans. In

particular, with respect to humans, there is no consistent evidence of delimited, noise-induced auditory deafferentation in humans. Specifically, it is currently unclear (1) what intensity level/durations of noise exposure cause synapse loss in humans, (2) whether and how much the human inner ear can recover from synaptic damage following noise exposure, and (3) whether some types of noise (e.g., impact/impulse exposures) are more likely to cause synapse loss than continuous noise.

3.3. Other factors related to hidden hearing Loss

3.3.1. Compounding effect of aging and noise exposure

The previous section may have given the impression that we now have a relatively detailed understanding of the consequences of age- and noise-related ANF-IHC loss and hair cell loss in animals. However, this is likely overstating our state of knowledge, since aging and noise exposure have a compound effect on the auditory system. CBA/J mice older than 8 weeks showed decreased vulnerability to noise exposure with aging (Henry, 1982). During the 'critical period' of weeks 4–8 after birth, CBA/CaJ mice are more vulnerable to noise exposure than when exposed at an older age. Severity level 2 noise exposure of 8–16 kHz octave band noise for 2 h causes TTS in adult CBA/CaJ mice, but PTS for CBA/CaJ mice in the critical period (Kujawa and Liberman, 2006). Immediately following severity level 3 noise exposure at week 16, CBA/CaJ mice showed more IHC-ANF synapse loss and OHC degeneration than controls at frequencies higher than the exposure frequency (Fernandez et al., 2015, 2020). One year later, the IHC-ANF loss had expanded to lower frequency regions (Fernandez et al., 2015; Kujawa and Liberman, 2009). Even cochlear regions that are seemingly unaffected by synapse or OHC damage (or fully recovered regions) show faster hair cell and synapse loss when animals age following noise exposure than in unexposed aging animals (Fernandez et al., 2015).

3.3.2. Inbred mouse strains

Different inbred strains of mice show different rates of IHC-ANF synapse loss. In addition to the CBA/CaJ mice mentioned above, the C57BL/6 strain has been studied intensively as a mouse model for presbycusis. The onset of age-related hearing loss is much earlier in C57BL/6 mice than in CBA/CaJ mice (Hunter and Willott, 1987), while C57BL/6 mice are also more vulnerable to noise exposure (Shone et al., 1991). Moreover, as was mentioned in 3.2.3, after severe level 3 noise exposure, the damage to IHC-ANF synapses of CBA/CaJ mice is permanent, while C57BL/6 mice can regrow these synapses after noise exposure (Kaur et al., 2019; Kim et al., 2019). The main deficit of the C57BL/6 strain is genetic in nature (Johnson et al., 1997; Noben-Trauth et al., 2003), and it is not yet clear whether and how this genetic cause is related to age-related hearing loss in humans (Kujawa and Liberman, 2019). Nevertheless, this specific vulnerability of C57BL/6 mice might suggest that those who are more likely to suffer from age related auditory deafferentation (and thus HHL) might also be more vulnerable to noise induced auditory deafferentation (Shone et al., 1991). It is critical, however, to be cautious when generalizing results from a single mouse strain, given the significant variations between inbred strains.

3.3.3. Genetic causes of auditory deafferentation

Auditory deafferentation can also be caused by genetic mutations. Even though relatively little is known about which genes contribute to auditory deafferentation or even hearing loss, some genes that cause deafness instead of hidden hearing loss are found to be relevant to synaptopathy in the inner ear (Shearer and Hansen, 2019). A more in-depth discussion of genetic causes goes beyond the scope of this review; however, for a detailed review of the current knowledge on genetic causes of cochlear synaptopathy, see Shearer and Hansen (2019).

3.3.4. Auditory demyelination

So far, we have primarily focused on auditory deafferentation caused by the loss of auditory afferent channels (IHC loss, ANF loss or IHC-ANF synapse loss). However, auditory demyelination might also degrade the transmission of afferent information, and might thereby play an additional role in HHL (Choi et al., 2018; Wan and Corfas, 2017). Auditory demyelination refers to the loss of the myelin sheath surrounding ANFs, consequently reducing their spike transmission velocity, while demyelination might also impair the seminode of Ranvier, thereby affecting the generation of action potentials themselves (Wan and Corfas, 2017). Following severity level 4 noise exposure, the myelin around ANFs became thinner in CBA/CaJ mice, possibly due to damage to the Schwann cells that form the myelin sheath (Kurioka et al., 2016). In a study investigating the perceptual effects of auditory demyelination, human participants with a demyelination disease – Charcot-Marie-Tooth disease type 1A (CMT1A) – showed slightly worse speech perception in noise but comparable speech in quiet performance compared to a control group (Choi et al., 2018). Note, though, that the myelination deficit in CMT1A extends beyond the cochlea, i.e., it is not selective to ANF demyelination, and therefore does not allow the conclusion that the perceptual deficit in CMT1A is exclusively due to auditory demyelination. Moreover, human ANFs are largely unmyelinated, so it is unclear whether and how auditory demyelination induces hearing deficits in humans (Ota and Kimura, 1980). Nevertheless, these studies suggest that auditory demyelination, especially in rodents, is worth investigating in connection with behavioral deficits that resemble HHL-like symptoms.

4. How does the central auditory system react to changes in the periphery?

Following loss of peripheral input, the subcortical and cortical centers in the ascending auditory pathway adapt to the loss of afferent input, a compensatory process known as neural plasticity (Kolb and Whishaw, 1998). As such, the processing in subcortical and cortical centers is often described in terms of a gain with respect to the input-output function in the auditory system. Following auditory deafferentation, the gain at subcortical and cortical centers is increased, which is thought to represent a compensatory mechanism due to the loss of afferent information (Harris et al., 2022; Schaette and McAlpine, 2011). This gain can be assessed by different metrics such as the ABR wave 4/1 or V/I amplitude ratio (Möhrle et al., 2016; Schaette and McAlpine, 2011), a change in firing rate as a function of stimulus level in IC and auditory cortex (Chambers et al., 2016), or the amplitude of the cortical P1 response to clicks (Harris et al., 2022).

4.1. Subcortical adaptation to auditory deafferentation

The auditory pathway comprises multiple structures at the subcortical level. From the periphery to the midbrain, these structures include the cochlear nucleus (CN), the superior olivary complex (SOC), the lateral lemniscus (LL), the inferior colliculus (IC), and the medial geniculate body (MGB). These structures make up a more complex subcortical processing pathway than other sensory processing pathways, e.g., the visual pathway (King and Nelken, 2009). As such, they perform complex analyses related to sound localization (Grothe et al., 2010), sound characterization (Pannese et al., 2015), or selective attention (Forte et al., 2017).

One of the most direct ways to investigate the electrophysiological changes in the subcortical and cortical auditory nervous system following deafferentation is multi-unit recording, which simultaneously records action potentials from multiple neurons. Some studies suggest that the spontaneous rate of neurons is elevated in IC following severity level 4 noise exposure that caused PTS in guinea pigs (Coomber et al., 2014) and CBA/J mice (Ma et al., 2006). For severity level 3 noise exposure, it remains unclear how the spontaneous rate changes in IC, since Hesse et al. (2016) showed an increased IC spontaneous rate in CBA/Ca mice, while the spontaneous rate in CBA/CaJ mice in Shaheen and Liberman (2018) was unaffected. An increase in the steepness of the

slope of the rate-level function of IC neurons has also been reported (Shaheen and Liberman, 2018), suggesting an increased central gain in mice after noise-induced auditory deafferentation. Similarly, Heeringa and Van Dijk (2014) found the spontaneous rate of IC neurons in guinea pigs unaffected after severity level 3 noise exposure, but observed a sustained reduction in inhibitory activity and an increase in excitatory activity in IC.

The IC is able to adapt to input changes over time. While behavioral tone detection in quiet remains normal, IC neurons in CBA/CaJ mice showed a drop in the firing rate to tones in silence, a threshold shift, and a smearing of their frequency tuning curves seven days after a ouabain induced loss of 95% of SGNs (Chambers et al., 2016). All these measures were shown to have recovered, albeit not fully, after 30 days (Chambers et al., 2016). Similarly, the classification of consonant-vowel-consonant (CVC) speech tokens, based on the recorded neuronal response in IC, was impaired instantly, but partially recovered after 30 days (Chambers et al., 2016). This suggests that after near-total ablation of auditory afferents, the subsequent impact on coding (as evidenced by decreased classification accuracy and a reduced response to tones) at the IC is only temporary. Instead, neuro-plastic changes occurring over time manage to progressively adapt the gain at the subcortical processing centers to compensate for the peripheral loss such that near-normal levels of performance are eventually recovered.

This change in IC coding also varies with stimulus level. CBA/CaJ mice show less IC adaptation to loud noises after severity level 3 noise exposure than unexposed control mice (Bakay et al., 2018). In gerbils, after severity level 3 noise exposure, the classification of vowel-consonant-vowel (VCV) tokens was more accurate for low (60 dB SPL) compared to high (75 dB SPL) stimulus presentation levels (Monaghan et al., 2020). This difference in classification performance suggests that subcortical processing is selectively affected by noise-induced auditory deafferentation: even though the gain in IC compensates for the loss of afferents at low sound levels, and possibly even over-compensates (i.e., too much gain is applied), this change in gain cannot fully restore sound differentiation abilities in noise at high sound levels.

In conclusion, studies in animals suggest that auditory deafferentation triggers some level of adaptation or plasticity at the level of the IC, but this plasticity cannot fully compensate for the loss to its pre-deafferentation level based on speech token classification. There have not been many animal studies that have investigated other subcortical structures (e.g., CN or MGB) in conjunction with deafferentation. More research is therefore needed to better characterize the subcortical changes after auditory deafferentation over time, and how these changes might relate to perception in both animals and humans.

4.2. *Cortical adaptation to auditory deafferentation*

The final subcortical processing center, the MGB in the thalamus, conveys its information to the auditory cortex (AC). The AC consists of six, functionally different layers: layers 1–3 process intracortical information; layer 4's main input is from the thalamus; layers 5 and 6 form a corticofugal pathway and project back to subcortical regions (Kanold et al., 2014; Read et al., 2002; Smith and Populin, 2001).

The gain in cortical local field potentials depends on the severity of auditory deafferentation. Chinchillas treated with different dosages of carboplatin, which selectively ablates IHCs and IHC-ANF synapses, showed persistent hypoactivity in both compound action potentials and local field potentials in the IC (Qiu et al., 2000; Salvi et al., 2017). In contrast, the AC showed initial temporary hyperactivity in the evoked response two weeks post-treatment, before this hyperactivity turned into hypoactivity five weeks post-treatment, particularly if the deafferentation exceeded 70%.

The effect of auditory deafferentation on the nervous system's encoding ability is also stimulus dependent. 30 days after ouabain induced 95% auditory deafferentation, sound level encoding of CBA/CaJ mice had fully recovered in AC, but not in IC (Chambers et al., 2016). However, the encoding of speech tokens remained impaired in both AC and IC.

One of the potential mechanisms underlying neuronal gain is the balance between excitation and inhibition (E-I balance), which is critical for cortical processing (Wehr and Zador, 2003). The different types of neurons in the AC can be broadly divided into excitatory and inhibitory neurons. Among these neurons, we will focus on excitatory pyramidal cells (Py cells), and inhibitory parvalbumin-expressing GABAergic cells (PV cells) (Maor et al., 2016). The traditional explanation for AC hyperactivity is that the loss of inhibitory neurons causes hyperactivity in excitatory neurons (Herrmann and Butler, 2021), as shown in Fig. 3. However, a recent empirical study looked specifically at the changes in Py and PV neurons in AC following auditory deafferentation (Resnik and Polley, 2021). After an ouabain-induced loss of around 70% of SGNs, mice (of the C57BL/6 genetic background) immediately showed increased spontaneous activity in both Py and PV neurons in layers 2/3 of primary AC. While the spontaneous activity of Py neurons remained hyperactive twelve days after ouabain treatment, the activity of PV neurons had returned to normal. At the moment, comparatively little is known about the neural circuitry of Py and PV neurons in the auditory cortex of mice (which would allow a more detailed assessment of the impact of this finding). Nonetheless, the fact that inhibitory PV neurons were initially hyperactive and subsequently returned to normal levels of spontaneous activity (as opposed to reverting to reduced or even absent levels of activity) suggests that the neural circuitry underlying cortical hyperactivity is more complex than the mere absence of inhibitory signals.

In addition, the ouabain-treated mice, with a 70% loss of SGNs, had more missed trials compared to control mice in a tone detection in noise task. These missed trials were characterized by hyperactivity and hyper-synchronization of Py neurons in the ~500 ms period preceding the presentation of the tone (Resnik and Polley, 2021). This hyperactivity might be explained by the hyperexcitability of the cortical neural network following almost complete auditory deafferentation (Houweling et al., 2005), although so far little is known about the circuits leading to the hyperactivity and hyper-synchronization. The presence of such hyper-synchronization, along with its correlation to behavioral target detection, suggests that auditory deafferentation might be a distal trigger instead of the primary cause of hearing deficits in noisy environments.

Even though auditory deafferentation is an important potential cause

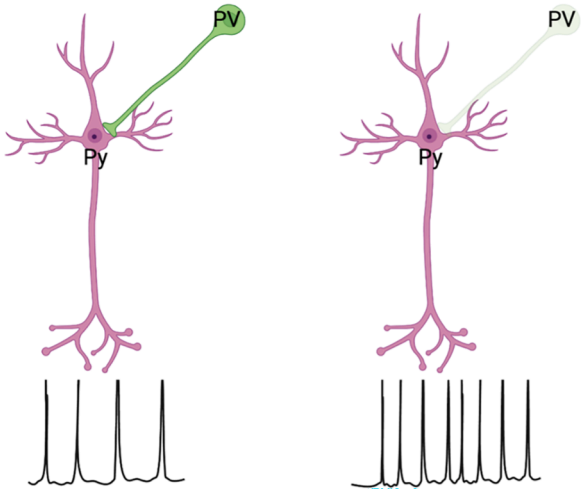

Fig. 3. Putative cause for hyperactivity in the auditory cortex after hearing loss: The loss of inhibitory PV cells following auditory deafferentation gives rise to hyperactivity in Py neurons, indicated as an increased spike rate in the black trace below (figure adapted from Herrmann and Butler 2021). However, recent findings suggest that this might be an oversimplification (Resnik and Polley, 2021).

of HHL, there are relatively few studies in humans that have investigated the associated cortical changes following auditory deafferentation. A couple of recent studies utilized cortical evoked potentials (measured using EEG) to investigate the cortical adaptation to potential auditory deafferentation, including the P1, N1, and P2 components (Bramhall et al., 2020; Harris et al., 2022). The P1, or P50, is a positive event-related component with a latency of around 50 ms post stimulus onset, and is thought to be generated in primary auditory cortex. Similarly, N1 and P2 are negative and positive deflections with latencies of approximately 100 ms and 200 ms, respectively; their generators are thought to be in secondary and association auditory cortices (Lightfoot, 2016). Both older adults and young military veterans with noise exposure had smaller P1 and slightly stronger N1 and P2 magnitudes compared to young adult controls (Bramhall et al., 2020; Harris et al., 2022). Harris et al. also measured GABA (an inhibitory neurotransmitter) levels of their participants and showed that higher GABA levels correlated with better speech perception in noise performance.

There are several factors that are challenging for the investigation of cortical changes following auditory deafferentation in humans: first, there is presently no accepted measurement for diagnosing auditory deafferentation in humans (Guest et al., 2019b; Plack et al., 2016). Second, auditory deafferentation naturally co-occurs with other auditory deficits or factors, which are difficult to control. For example, the integrity of the cochlear lateral wall (which is important for maintaining the endocochlear potential) as well as OHCs and IHCs all naturally degrade with aging (Lang et al., 2010; Sergeyenko et al., 2013; Wu et al., 2019, 2020). Some cognitive abilities also decline with aging, which calls into question the power or appropriateness of complex auditory tests (Hoogendam et al., 2014). Third, the results in human studies have been mixed in terms of whether or not a particular peripheral or subcortical physiological measure (for example, the envelope following response (EFR) and ABR) correlates with risk factors (age and noise exposure) and predicted consequences (speech perception difficulties) of auditory deafferentation (see reviews in Bramhall et al. 2019, Bramhall 2021 for details).

In conclusion, auditory deafferentation in animals induces both hyperactivity and a lack of inhibition in the auditory cortex. However, these two changes might not be causally related to each other, and it is likely that hyperactivity and hypoactivity are not sufficient to fully characterize HHL. In animals, more research is needed to improve our understanding of the structural and functional changes in the cortex that occur secondary to auditory deafferentation. For studies in living humans, in which the actual number of IHC-ANF synapses cannot be determined, it is currently only possible to investigate the relationship between the subcortical/cortical responses and behavioral/perceptual measures. However, designing appropriate experiments and interpreting their results is not trivial, due to the difficulty of controlling cognitive and peripheral factors (e.g., working memory, auditory demyelination).

5. Do people notice hidden hearing loss?

Despite a considerable number of studies, some of the key questions regarding how HHL impacts hearing are still unanswered. How much does HHL affect communication? At which level of auditory deafferentation does HHL become noticeable? Do people even notice HHL?

Computational models provide some insights into how perception might be affected by auditory deafferentation. Based on computations drawing on signal detection theory, the relationship between a change in detection threshold in quiet and auditory deafferentation follows Eq. (1) (Oxenham, 2016). This prediction suggests a considerable redundancy in the auditory system, since a large range of auditory deafferentation levels would only cause a relatively minor change in the detection threshold. For example, the model predicts that 50% auditory deafferentation only leads to a 1.5 dB shift in detection threshold in both noisy and quiet backgrounds, while even at 90% auditory deafferentation the threshold shift would still only be 5 dB. These model predictions align with empirical findings in chinchillas (Lobarinas et al., 2013).

$$\textit{Threshold increase}\ (\mathrm{dB}) = 5 \times \log_{10}\left(\frac{\textit{total ANF count}}{\textit{ANF survival count}}\right) \qquad \text{(Eq. 1)}$$

However, a recent study in mice (Resnik and Polley, 2021) found that the cost of auditory deafferentation is different in silent vs. noisy listening conditions: whereas ~70% auditory deafferentation yielded no detectable behavioral threshold shift in silence, it resulted in an 18 dB tone detection threshold shift in noise (the hallmark pattern of HHL). This perceptual cost was based on mouse (C57BL/6J background) behavioral detection thresholds, while the perceptual cost predicted by signal detection theory was based on the ANF response to sound. This suggests that the perceptual cost contributed by the peripheral loss alone (predicted based on signal detection theory) is less than the actual perceptual cost (based on the behavioral results in mice), possibly due to compound downstream changes. This discrepancy highlights a need for more investigation of the changes in subcortical and cortical processes following auditory deafferentation.

Despite the discrepancy with respect to tone detection deficits in the above-mentioned two studies, both studies nevertheless demonstrate how robust the mammalian hearing system is in detection tasks. However, tone or signal detection tasks are rather simple in nature, which begs the question of whether there are more ecologically meaningful consequences of auditory deafferentation, for example with respect to speech perception.

In an attempt to investigate more complex perceptual changes due to auditory deafferentation in humans, studies have focused on the relationship between speech perception difficulties in noise and risk factors of auditory deafferentation, e.g., age and noise exposure (in individuals with clinically normal hearing). However, while some studies have shown that decreased speech perception in noise correlates with normal aging (Füllgrabe et al., 2015; Garrett et al., 2020; Presacco et al., 2019), others found no evidence for such a relationship (Johannesen et al., 2019; Prendergast et al., 2019). For detailed reviews on the relationship between noise exposure and speech perception in noise, see DiNino et al. (2022) and Le Prell (2019). One factor that might contribute to these inconclusive results is the degree of auditory deafferentation, which was likely highly variable across participants in these studies. Similarly, if the three types of ANFs are differentially affected, this might also affect HHL to different degrees. These aspects, which currently cannot be determined precisely in humans, present significant challenges to investigating speech perception deficits that are related to auditory deafferentation.

Another potential reason for these conflicting findings might be that speech in noise performance seems to be task dependent. Specifically, in their review, DiNino et al. (2021) found that tasks with less contextual, lexical, and semantic cues were more likely to reveal a deficit in participants with higher degrees of estimated auditory deafferentation. More importantly, speech reception thresholds alone might be too crude to reveal auditory deafferentation-related changes. A recent study showed that while digit recognition in noise performance was similar between a group of people with high levels of noise exposure and a control group, people with high levels of noise exposure needed to recruit substantially more listening effort to achieve this level of performance (Degeest et al., 2022). In conclusion, the nature of speech perception tasks and the degree of listening effort should be considered in the design of future studies that investigate the perceptual consequences of auditory deafferentation.

6. How can we diagnose hidden hearing loss?

In the past decade, a large effort in both animal research and human research has been devoted to finding a diagnostic marker for auditory

deafferentation (Bharadwaj et al., 2019; Bramhall, 2021; Bramhall et al., 2021; Grant et al., 2022; Guest et al., 2019a; Kamerer et al., 2019). Recent findings suggest that the auditory brainstem response (ABR) (Bramhall, 2021), the envelope following response (EFR) (Mepani et al., 2021; Van Der Biest et al., 2023), and the middle ear muscle reflex (MEMR) (Bharadwaj et al., 2022; Trevino et al., 2023) might be promising candidates for an objective characterization of HHL.

6.1. Auditory brainstem response and electrocochleography

The ABR is used as a physiological indicator of the functioning of the auditory nerve and subsequent subcortical regions. The ABR, as recorded via surface electrodes attached to the head in response to brief sounds such as tone pips or clicks, consists of multiple waves or peaks that are labeled based on their respective order of occurrence (see Fig. 4). Each ABR wave is thought to originate in different centers of the early auditory pathway (however, the generator-ABR wave correspondence differs slightly between species). Human ABR waves are generally numbered via Roman numerals I–V, while animal ABR waves are usually denoted using Arabic numerals 1–5 to emphasize that the generators of individual waves are different compared to those in humans. The small shoulder proceeding wave I (or wave 1) is typically referred to as the summating potential (SP). The SP is thought to be generated by inner hair cells (Zheng et al., 1997). Wave 1 is thought to capture the response from the auditory nerve (Møller AND Jannetta, 1983), while wave 2 is estimated to be generated by the auditory nerve and/or CN (Tait et al., 1987). Wave 3 is thought to be generated by the CN, wave 4 likely originates in SOC and LL, and wave 5 is thought to be generated from the LL and IC (Land et al., 2016; Moore, 1987; Parkkonen et al., 2009).

Similar to wave I (or wave 1), the compound action potential (CAP) obtained with electrocochleography (ECochG) records the response to sound in the auditory nerve (Lee et al., 2019). ECochG and ABR differ with respect to the recording site: the ABR is recorded from the scalp (Skoe and Kraus, 2010), while the ECochG is recorded from the ear canal, often using a tiptrode in humans (Eggermont, 1976). Note, however, that the usage of these two terms is not clearly delineated, since some authors refer to the tiptrode recorded signal as ABR (Bramhall et al., 2017; Prendergast et al., 2018; Washnik et al., 2020), while others refer to it as ECochG (Barbee et al., 2018; Grinn et al., 2017). The amplitude and latency of ABR wave 1 and CAP reflect the degree of synchronization in the ANFs. Specifically, the more synchronized the ANFs' response to a sound, the shorter the latency and the larger the magnitude. Based on data from gerbils (Bourien et al., 2014), the threshold and amplitude of ABR wave 1 (or CAP) are determined by two different subgroups of ANFs: the threshold is determined by high-SR fibers, while the amplitude is mainly determined by high- and medium-SR fibers. It follows that the loss of low-SR ANFs cannot be captured by ABR wave 1 or CAP.

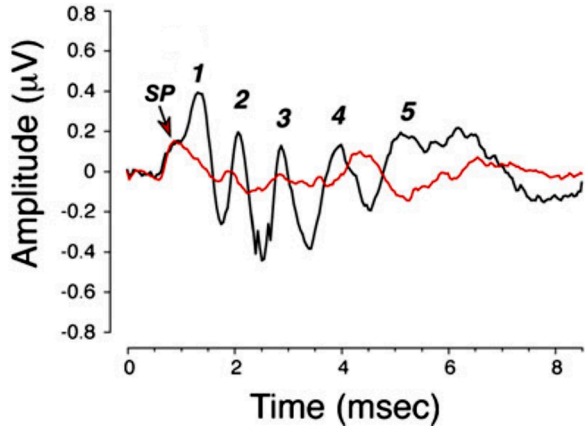

Fig. 4. ABR wave before (black) and after ouabain application (red) of CBA/CaJ mice. Note that only SP wave (from IHCs) is preserved following the ouabain application (figure from Yuan et al. 2014).

The ABR wave 1 is widely used in animal studies as a physiological indicator of the health of the auditory nerve. The ABR threshold deteriorates with aging in CBA/CaJ mice (Kujawa and Liberman, 2006; Sergeyenko et al., 2013), rats (Möhrle et al., 2016), gerbils (Heeringa et al., 2020), cats (Harrison and Buchwald, 1982) and rhesus monkeys (Fowler et al., 2010). Similarly, wave 1 (or wave I) amplitude decreases and its latency increases with aging in mice and humans (Burkard and Sims, 2002; Grose et al., 2019; Konrad-Martin et al., 2012; Lotfi and Abdollahi, 2012; Sergeyenko et al., 2013). In drug-induced auditory deafferentation, the ABR threshold is also elevated, with a reduced wave 1 amplitude (Lobarinas et al., 2013; Resnik and Polley, 2021; Yuan et al., 2014). In response to a severity level 3 noise exposure, the ABR in mice often shows a TTS, which fully recovers over time (Fernandez et al., 2015; Kujawa and Liberman, 2009). The amplitude of ABR wave 1 is reduced after severity level 3 noise exposure in CBA/CaJ mice (Fernandez et al., 2015). However, whether or not ABR wave I amplitude also correlates with noise exposure in humans is currently unclear. While some studies find that they are correlated (Bramhall et al., 2017; Grose et al., 2017; Stamper and Johnson, 2015), others do not (Fulbright et al., 2017; Prendergast et al., 2019; Washnik et al., 2020). For a more in-depth review of ABR changes that might be related to noise exposure history, refer to Le Prell (2019) and Bramhall (2021).

Another ABR wave that is often used in addition to wave I (or wave 1) is ABR wave V (or wave 5). While the amplitude of wave 1 decreases with aging, the amplitude of wave 5 remains stable (Harrison and Buchwald, 1982; Möhrle et al., 2016). In addition, wave V amplitude is unaffected by high noise exposure in humans (Bramhall et al., 2017) or by severity level 3 noise exposure in CBA/CaJ mice (Hickox and Liberman, 2014). It is thought that this is due to plastic changes in gain in subcortical regions prior to, and including IC (Schaette and McAlpine, 2011; Sergeyenko et al., 2013). Furthermore, since the latency and the amplitude of both wave I (or wave 1) and wave V (or wave 5) show large inter-individual variability, the ratio of wave V (or wave 4 in rodents) vs. wave I (or wave 1) is sometimes suggested to be a more robust physiological indicator. This ratio differs significantly between young and aged animals (Möhrle et al., 2016; Sergeyenko et al., 2013), and between humans with low and high noise exposure levels (Bramhall et al., 2017; Prendergast et al., 2018). Similarly, the ratio between SP and wave I might also be useful for indicating auditory deafferentation (Grant et al., 2022; Liberman et al., 2016). However, the test-retest reliability of the SP/wave I ratio is lower than that of the wave V/I ratio (Prendergast et al., 2018). Moreover, it should be mentioned that these ratio-based measures are not pure indicators of auditory deafferentation. For example, the wave V/I ratio (or wave 4/1 ratio) is also an indicator of central gain (see Section 4). This complicates the interpretation of these measures.

For a measure to be useful clinically for the diagnosis of auditory deafferentation or HHL, it needs to be reliable. Unfortunately, the reliability of ABR wave I is relatively low across human participants (Mehraei et al., 2016; Prendergast et al., 2018). A recent review by Bramhall (2021) summarizes the factors that can affect the quality of ABR recordings and the amplitude of ABR wave I in humans, such as different recording methods, different elicitors of ABR wave I, and coexisting OHC dysfunction. Bramhall (2021) suggests necessary next steps and best practices so that recording the ABR wave I can be useful clinically in helping to diagnose auditory deafferentation.

As mentioned in Section 3.3.4, auditory demyelination might also lead to auditory deafferentation. Demyelination has been shown to reduce the ABR wave 1 amplitude and to delay wave 1 in mice (C57BL/6J background) (Wan and Corfas, 2017). Data from mice (C57BL/6J background) and a recent computational model further suggest that wave 1 latency is only affected by demyelination, but not by ANF loss (Budak et al., 2021; Wan and Corfas, 2017). Additionally, an increase in latency of ABR wave I (or wave 1) is sometimes also observed in auditory

deafferentation studies, suggesting the possible co-existence of demyelination in addition to IHC-ANF synapse loss (Budak et al., 2021; Garrett and Verhulst, 2019; Zhang et al., 2017). Additionally, OHC dysfunction also leads to delayed ABR wave 1 latency and reduced ABR wave 1 amplitude, even without causing a significant shift in thresholds (Sergeyenko et al., 2013). The potential impacts of demyelination and OHC dysfunction on ABR wave I raises concerns about its reliability as a diagnostic marker for auditory deafferentation.

In conclusion, research in animals suggests that the ABR should be explored further as a possible physiological indicator of auditory deafferentation. However, how well these findings in animals can be translated to a diagnosis in humans, and whether a particular ABR wave I amplitude cutoff can be determined as the diagnostic threshold for auditory deafferentation, remains unclear. Moreover, most of the animal studies show such results at a group level, thus limiting the utility of the ABR as a diagnostic tool for characterizing the degree of auditory deafferentation in individuals.

6.2. Envelope following response

The envelope following response (EFR) describes the scalp-recorded response from the auditory system to an amplitude-modulated (AM) sound, and as such indicates how well the auditory system tracks or phase locks to temporal changes in the stimulus amplitude envelope. The EFR can originate from different auditory stations, including the auditory nerve, the brainstem, the thalamus, and the auditory cortex (Parthasarathy and Kujawa, 2018; Shaheen et al., 2015). The preferred AM rate of a given structure decreases along the ascending auditory neuroaxis (Joris et al., 2004), and changing the modulation frequency of the AM sound can therefore capture the EFR generated in different auditory processing centers. For example, in mice the EFR to an AM sound with a modulation frequency between 2 and 4 kHz is thought to originate from inner hair cells, while the EFR to a ~1 kHz AM frequency is assumed to be contributed primarily by the auditory nerve (Parthasarathy and Kujawa, 2018).

After ouabain-induced auditory deafferentation in CBA/CaJ mice, the EFR to a sinusoidal AM sound with a modulation frequency of 1 kHz is reduced compared to control mice (Parthasarathy and Kujawa, 2018). With aging, the EFR amplitude in mice also decreases (Parthasarathy and Kujawa, 2018). Following a severity level 3 noise exposure in CBA/CaJ mice, the EFR to a 1 kHz sinusoidal modulator shows a significant reduction in amplitude compared to control mice (Shaheen et al., 2015).

In humans, an EFR to a sound with a modulation frequency of ~40 Hz likely originates in the auditory cortex, while an EFR to a modulation frequency of around 110 Hz is thought to be contributed mainly by subcortical structures (Parthasarathy et al., 2019; Ross et al., 2003). As straightforward as this mapping seems, an EFR to a modulation frequency of 1 kHz (presumably from ANFs) is very hard to capture in humans because the response at such high modulation frequencies often does not exceed the noise floor of the recordings made with non-invasive scalp electrodes (Purcell et al., 2004; Tichko and Skoe, 2017). Nevertheless, since the loss of afferents in the auditory system impairs its temporal fidelity (Grose et al., 2017), an impaired EFR at the subcortical or cortical level might indicate the existence of auditory deafferentation at the cochlear level.

In addition to differences in modulation frequencies, the wave shapes of modulators and the types of carriers have also been explored in search for a more sensitive stimulus setup to detect auditory deafferentation. Some studies have used sinusoidal modulation of pure tone carriers (Bharadwaj et al., 2015; Bramhall et al., 2021; Paul et al., 2017a; Prendergast et al., 2017a, 2019) or noise carriers to evoke EFRs (Irsik et al., 2021), while others have employed rectangular modulators (Mepani et al., 2021; Vasilkov et al., 2021). The carrier frequency also varies across studies, as well as the modulation depth (Bharadwaj et al., 2015; Bramhall et al., 2021). In a recent computational modeling study that aimed to find an optimal set of EFR parameters for detecting auditory deafferentation (Vasilkov et al., 2021), the amplitude of the EFR was shown to differ between stimulus parameters such as carrier type (noise versus tone), duty cycle, and modulation shape. The EFR was most sensitive to auditory deafferentation when the stimulus consisted of rectangular amplitude-modulated tones with 95% modulation depth and a 25% duty cycle (Vasilkov et al., 2021). This might be because higher modulation depth, lower duty cycle and rectangular modulator could cause a more synchronized response from the auditory pathway. A higher EFR magnitude with this parameter set also correlated with better speech perception in noise (Mepani et al., 2021). Veterans with significant noise exposure history have also been shown to have a reduced EFR amplitude (sinusoidal modulation at 110 Hz) compared to non-veterans (Bramhall et al., 2021), while recreational noise exposure (sinusoidal modulation at 80 Hz) or self-reported noise exposure history (sinusoidal modulation from 240 to 285 Hz) does not seem to have a similar effect (Grose et al., 2017; Prendergast et al., 2017a). Moreover, young normal hearing participants with self-reported high noise exposure showed less resistance to background noise as measured with the EFR (sinusoidal modulation at 86 Hz), suggesting that the presence of noise may exacerbate auditory deficits in individuals with elevated levels of noise exposure (Paul et al., 2017b).

More research is needed on the relationship between the EFR and human noise exposure history to better understand noise-induced auditory deafferentation in humans and the potential of the EFR as an electrophysiological indicator of auditory deafferentation. Nevertheless, the facts that (1) the EFR amplitude is one of the most robust electrophysiological measures that might indicate auditory deafferentation in humans with regard to test-retest reliability (Guest et al., 2019b), and that (2) it might be less sensitive to OHC loss (Encina-Llamas et al., 2019), suggest that it might be a good candidate for the clinical diagnosis of auditory deafferentation.

6.3. Middle ear muscle reflex

The middle ear muscle reflex (MEMR) is an important subcortical feedback reflex that suppresses incoming sounds at the level of the middle ear bones. Information about high-intensity sounds is processed in the CN and then sent back to the middle ear, causing the middle ear muscles to constrict and thereby dampen the movement of the middle ear bones. The MEMR attenuates either the sound from the outside environment or self-generated noise like chewing (Mukerji et al., 2010), and is thought to receive input specifically from afferent ANFs, which might make it a good physiological indicator of ANF survival (Parthasarathy et al., 2019; Valero et al., 2016).

In CBA/CaJ mice that underwent severity level 3 noise exposure, both MEMR magnitude and threshold in response to a probe of an upsweep chirp (2 s, 4 to 32 kHz) correlate more strongly with cochlear synaptopathy than the ABR wave 1 does (Valero et al., 2018). Similarly, chinchillas show elevated MEMR thresholds (elicited by wideband noise and probed by a click) following severity level 3 noise exposure (Bharadwaj et al., 2022). The MEMR has been shown to be a very reliable measure in humans (Guest et al., 2019b; Kamerer et al., 2019). Furthermore, the MEMR is also relatively less sensitive to OHC loss or pure tone threshold elevation in individuals with clinically normal hearing thresholds (Bramhall et al., 2022). These features of MEMR therefore lend themselves well for clinical diagnosis of auditory deafferentation. However, the MEMR's ability to detect auditory deafferentation may depend on the specific probe used for measuring the MEMR. Studies using a wideband probe (e.g., a click) found that MEMR amplitude, growth function or threshold correlates with age (Bharadwaj et al., 2022), chronic tinnitus (Wojtczak et al., 2017), history of high noise exposure (Bharadwaj et al., 2022; Bramhall et al., 2022; Shehorn et al., 2020) and single-word recognition in noise (Mepani et al., 2020) in normal hearing humans. Conversely, other studies that used 226 Hz probes found no correlation between the MEMR threshold and speech

perception in noise or noise exposure history (Guest et al., 2019b; Saiz-Alía et al., 2019). Since the standard probe in clinical settings is typically a 226 Hz pure tone, it has been suggested that adding a wideband probe to the procedure might make MEMR measurements more sensitive to potential signs of auditory deafferentation (for a detailed discussion, see Bharadwaj et al. 2019).

6.4. Conclusions

So far, a gold standard non-invasive measure for auditory deafferentation remains elusive, even with a progressively clearer view of which measures might be potential candidates. Without knowing the actual degree of auditory deafferentation in living humans, it remains challenging to find a proxy physiological measure that correlates sufficiently well with auditory deafferentation. This is reflected in the fact that the above-mentioned proposed physiological indicators of auditory deafferentation were not consistent in their relationship with risk factors for auditory deafferentation (Gómez-Álvarez et al., 2023; Guest et al., 2019a; Parthasarathy et al., 2020; Prendergast et al., 2017a, 2019; Saiz-Alía et al., 2019). Moreover, many of these measures only reveal significant differences at a group level, which is not sufficient for individual diagnoses. Currently, a more achievable goal, rather than finding a single gold standard metric for auditory deafferentation, might be to identify a combination of measures (e.g., including speech perception difficulties, EFR, ABR and MEMR) that have been shown to indicate the likelihood or degree of auditory deafferentation. It should be noted that speech perception difficulty in noise itself is not a particularly helpful indicator of auditory deafferentation, since it can be related to other types of auditory dysfunction (Hunter et al., 2020; Vermiglio, 2014) or cognitive dysfunctions (Porto et al., 2023). Recent research has used advanced computational methods (individually optimized auditory models and neural networks) to classify the profile of auditory deafferentation combining EFR, audiogram, and distortion product otoacoustic emissions (Keshishzadeh et al., 2021) or to use EEG to classify participants' tinnitus (Liu et al., 2021). Combined risk factors like these might then help guide prevention or treatment.

7. Is there a treatment or prevention for IHC-ANF synapse loss?

Neurotrophin-3 (NT-3), a neurotrophic factor that supports the growth of new synapses and neurons (Klein et al., 1994), has been suggested to prevent ANF loss and subsequent SGN loss in deafness or cochlear implantation in guinea pigs (Budenz et al., 2012; Staecker et al., 1996). It has also been shown to help mice recover IHC-ANF synapses after noise exposure (Suzuki et al., 2016; Wan et al., 2014) and to prevent synapse loss with aging (Cassinotti et al., 2022).

Considering that there is currently no FDA-approved drug to treat hearing loss, such treatment in humans, if proven to be appliable and effective, could then benefit the large part of the general population that is expected to suffer from noise-induced or age-related auditory deafferentation. It might also help prevent the development of more severe hearing loss later in life (Cassinotti et al., 2022). However, there are a number of challenges that need to be addressed before NT-3 can be developed into a new drug. For example, the delivery method of NT-3 seems to affect the treatment outcome: with round window delivery of NT-3, only 7 out of 15 mice showed a near full recovery of IHC-ANF synapses following noise exposure (Suzuki et al., 2016), while transgenic overexpression of NT-3 led to a more reliable and consistent recovery across individual mice (Cassinotti et al., 2022). Whether a sustained release of NT-3 via an injectable hydrogel has the same prevention or treatment effect as NT-3 overexpression currently remains unclear (Wang et al., 2021). Moreover, it is unknown whether the treatment effects seen in mice would also hold in humans.

Recent studies have made substantial progress in the search for a pharmacological treatment for auditory deafferentation such that future studies might indeed reveal a breakthrough solution for treating or preventing noise-induced and age-related hearing loss following auditory deafferentation. In the meantime, hearing aids or assistive listening devices with noise reduction algorithms that increase the signal-to-noise ratio in some everyday hearing situations (Aubreville et al., 2018; Park and Lee, 2016) are a viable alternative for people with hearing difficulties in noise.

8. Discussion

In the past decade, auditory deafferentation, especially cochlear synaptopathy, has been identified as a potential cause of HHL. Animal studies have contributed significantly to an improved understanding of the physiological consequences of auditory deafferentation, such as a reduction in amplitude of the ABR wave 1, EFR, and MEMR. Human studies have mainly focused on identifying a correlation between behavioral/electrophysiological measures (e.g., speech perception in noise, EFR, ABR, MEMR) and risk factors of auditory deafferentation (e.g., noise exposure and age). Here, we have attempted to synthesize the findings in the literature to date, providing an overview of some of the key questions and corresponding answers around auditory deafferentation.

Until now, the majority of animal studies on auditory deafferentation have focused on the structural and physiological changes in the cochlea or in early subcortical processing centers. Their quantitative relationship is now well established in mice (Fernandez et al., 2020; Parthasarathy et al., 2019; Sergeyenko et al., 2013). However, there is increasing evidence that neural processing in the midbrain and cortical centers is also affected by auditory deafferentation (Chambers et al., 2016; Resnik and Polley, 2021), similar to the known role that cortical processes play in adapting to other peripheral changes, such as the fitting of cochlear implants or hearing aids (Fallon et al., 2008; Giroud et al., 2017; Herrmann and Butler, 2021). A better understanding of central auditory changes secondary to auditory deafferentation may explain the mixed results in human studies that examine the relationship between physiological indicators of deafferentation and measures of auditory perception.

To date, the data from humans remain inconsistent, especially for noise-induced auditory deafferentation. A main challenge in human auditory deafferentation studies is the absence of a gold standard diagnostic measure. This limits researchers to broadly search for any correlation between risk factors (age and noise exposure), noninvasive measures (e.g., ABRs, MEMR, EFR), and predicted consequences (speech perception difficulties) of auditory deafferentation. Despite a considerable effort across many different labs, no clear picture has yet emerged. To obtain a reliable indirect diagnosis of auditory deafferentation, other contributing factors will likely need to be considered, such as test-retest reliability (Guest et al., 2019b; Kamerer et al., 2019), exclusion of effects due to OHC loss (Wu et al., 2020), auditory demyelination (Budak et al., 2021; Wan and Corfas, 2017), or auditory efferent synaptopathy (Qian et al., 2021). So far, no test satisfies all these requirements. Considering the current mixed findings in terms of a diagnosis of auditory deafferentation, a combination of several tests will likely be needed to indicate the likelihood of cochlear synaptopathy in humans; for example, a combination of a speech-in-noise task (DiNino et al., 2021), EFR (Mepani et al., 2021) and MEMR (Bharadwaj et al., 2022) recordings, as well as high-frequency audiometric threshold measurements (Lokwani and Prabhu, 2022) could potentially guide further treatment.

Additionally, the relationship between auditory deafferentation and other auditory deficits needs further consideration, as well as the direct consequences of auditory deafferentation. So far, no direct correlation has been shown to exist between auditory deafferentation and a higher likelihood of acquiring sensorineural hearing loss later in life (Trevino and Lobarinas, 2022). Nevertheless, characterizing auditory deafferentation is critical so that its relationship to downstream changes in the auditory system and the functional consequences of those changes

may be better understood.

In this review, our focus has been on the causes and consequences of perceptual difficulties in noisy environments that are not accompanied by clinically abnormal audiometric thresholds. As we have outlined above, auditory deafferentation is one potential cause of HHL that has received a lot of attention in the past decade and a half. It is worth mentioning that auditory deafferentation has also been linked with another auditory dysfunction, tinnitus (Schaette and McAlpine, 2011; Vasilkov et al., 2023). Similar to HHL, the main risk factors for developing tinnitus include noise exposure and age (Elgoyhen et al., 2015; Jarach et al., 2022; Shore and Wu, 2019). As mentioned in Section 2.2, auditory deafferentation is a promising tool to study the plasticity of the auditory system in response to neurophysiological insult, both in regards to HHL and tinnitus.

In conclusion, the study of auditory deafferentation as a potential cause of HHL is still an active field of research. Due to the recent advances in knowledge gained from both animal and human studies, the field is moving closer to a diagnosis and treatment of auditory deafferentation. There are reasons for optimism that the next ten years in HHL research will yield a much-improved understanding of the causes and consequences of auditory deafferentation, and that this knowledge can be used to significantly increase the quality of life of the large part of the population that suffers from noise-induced or age-related hearing loss.

CRediT authorship contribution statement

Jiayue Liu: Writing – review & editing, Writing – original draft, Conceptualization. **Joshua Stohl:** Writing – review & editing. **Tobias Overath:** Writing – review & editing, Supervision, Conceptualization.

Data availability

No data was used for the research described in the article.

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