

Hidden Hearing Loss (Cochlear Synaptopathy): Diagnostic Challenges and Emerging Tests

Singh, A.K¹, Singh, A²

¹Anoop Kumar Singh, Audiologist and Speech-Language Pathologist.

²Ashutosh Singh, Audiologist and Speech-Language Pathologist.

Abstract

Hidden hearing loss (HHL), often attributed to cochlear synaptopathy, is characterized by difficulty understanding speech in noisy environments despite clinically normal pure-tone thresholds. Moderate noise exposure or aging may destroy synapses between inner hair cells (IHCs) and auditory nerve fibers (ANFs) without hair-cell death, leading to permanent deafferentation [1,2,3]. This neural loss degrades suprathreshold neural coding (e.g., reduced ABR wave I amplitude, impaired envelope-following responses [EFR]) and may manifest as speech-in-noise deficits, tinnitus, or hyperacusis [4,5,6]. However, diagnosing HHL is challenging: standard audiometry is insensitive to synaptopathy, and no consensus diagnostic criteria exist [7,8,9]. Emerging objective measures—reductions in ABR wave I, anomalies in EFR/FFR (frequency-following response), attenuated middle-ear muscle reflexes (MEMR), and altered electrocochleography (ECochG) SP/AP ratios—show promise as biomarkers of synaptopathy [10,11,12,13]. This review covers the neurobiological basis of cochlear synaptopathy, findings from animal and human work, the status of electrophysiological diagnostics (ABR, EFR/FFR, MEMR, ECochG), clinical implications for audiologists and neuroscience researchers, and future directions including standardized test batteries and possible therapies.

INTRODUCTION

Understanding speech in challenging listening environments is a common complaint even among individuals whose pure-tone audiograms fall within “normal” limits (e.g., ≤ 25 dB HL). A significant subset of such individuals report persistent difficulty in noise despite normal thresholds [14,15]. This phenomenon, termed hidden hearing loss (HHL), has been linked to cochlear synaptopathy—i.e., the loss of synaptic contacts between inner hair cells (IHCs) and ANFs [16,17,18]. Animal work reveals that moderate noise exposure or age-related insults can irreversibly sever IHC–ANF synapses even when hair cells survive and thresholds remain unchanged [19,20]. In rodents, exposures that produce no permanent threshold shift (PTS) nonetheless destroy up to 50% of synapses, leaving hair cells intact [21]. The result is auditory deafferentation: diminished suprathreshold neural output with preserved quiet-threshold sensitivity [22].

Risk factors for cochlear synaptopathy include noise exposure (even moderate, recreational), aging (so-called “hidden aging”), ototoxic drugs, and metabolic insults (e.g., diabetes) [23,24,25]. For example, age-related synaptopathy has been documented in human temporal bones: auditory nerve fiber counts decline with age even among individuals with preserved hair-cell counts [27]. Clinically, HHL commonly co-exists with tinnitus or hyperacusis and may represent an early stage of sensorineural hearing loss (SNHL) [26]. Because standard audiometry and otoacoustic emissions often appear normal, many cases go

undetected, underlining the need for sensitive supra-threshold diagnostics [7,8].

This article proceeds to review the pathophysiology of synaptopathy, then discuss diagnostic challenges in living humans, outline emerging electrophysiological tools, and finally consider clinical implications and future research directions.

Pathophysiology

At the core of HHL is synaptic deafferentation of IHC–ANF connections. Ribbon synapses at the base of IHCs transfer glutamatergic signals to ANFs; noise exposure or aging triggers excitotoxic glutamate release, terminal swelling, and synapse elimination [30]. Selective vulnerability appears to affect **low-spontaneous-rate (low-SR) ANFs**, which are less responsive at low sound levels but critical for coding in high-background noise conditions [31]. Crucially, these synaptic losses often precede hair-cell death and threshold elevation. Indeed, full threshold shifts only occur after ~80–90% fiber loss [32,33].

Histological studies in animals show that synapse loss occurs rapidly after noise exposure (even within hours to days) and may persist long term—even when outer hair cells recover and thresholds normalize [34]. For example, Kujawa & Liberman (2009) demonstrated that in CBA/CaJ mice, a temporary threshold shift of ~30 dB produced nearly 50% synapse loss immediately, with no hair-cell loss, and permanent reduction in ABR amplitude [21]. A more recent noise-dose study showed synapse loss increases to ~50% at moderate exposures and then declines at very high exposures that produce hair-cell loss—suggesting complex relationships among dose, synaptopathy and hair-cell injury [21].

In humans, temporal-bone work by Viana et al. (2015) revealed age-related degenerative changes in auditory nerve fibers, even in the presence of intact hair cells [35]. Emerging human imaging and physiological data support the existence of neural deafferentation without classical threshold changes [16]. Additional cochlear changes accompany synaptopathy: cochlear-nerve fiber demyelination, reduced conduction velocity, and changes in cochlear mechanics have been reported [38]. Centrally, reduced afferent input may prompt increased central gain (amplification) in brainstem or cortical circuits, which has been implicated in tinnitus/hyperacusis [39]. This compensation may mask peripheral loss until later stages.

Together, the pathophysiology of HHL involves: (1) synaptic/nodal damage at the IHC–ANF interface, preferentially low-SR fibers; (2) preserved hair cells/hair-cell responses and normal thresholds; (3) degraded suprathreshold neural synchrony and coding (temporal, intensity, and envelope); (4) compensatory central plasticity; and (5) eventual risk of overt SNHL if deafferentation continues unchecked.

Diagnostic Challenges

Diagnosing cochlear synaptopathy in living humans is inherently difficult. By definition, HHL is “hidden”—standard pure-tone audiometry (250–8000 Hz) and even otoacoustic emissions (OAEs) often appear normal [40,41]. Patients often present with complaints of **speech-in-noise difficulties, increased listening effort, tinnitus or hyperacusis**, despite “normal” audiometric thresholds [42]. These symptoms, however, overlap with central auditory processing disorder (CAPD), cognitive aging, attention deficits, and otologic-vestibular comorbidities, complicating interpretation [43].

Another major challenge is the lack of a **gold-standard** diagnostic marker for synaptopathy in humans. The animal “gold standard” is post-mortem synapse counting, which is not feasible in vivo [44,45]. Instead, many non-invasive proxies (ABR, EFR, MEMR, ECoChG) have been proposed—but results

across studies are inconsistent [46]. For example, a systematic review of 21 studies concluded that while candidate measures exist, none yet reliably detect synaptopathy in individual human subjects [48].

Confounders abound: anatomical variation (head size, sex, cochlear length), inter-subject variability in suprathreshold responses, middle-ear status, high-frequency hearing loss (often undetected), background noise exposure recall, and cognitive/effort factors all reduce specificity [47]. For instance, a 2016 study of tinnitus patients with normal audiograms found no correlation between lifetime noise exposure and ABR wave I amplitude or EFR metrics, calling into question the translational fidelity of animal findings [19]. Another large cohort found that behavioral speech-in-noise deficits correlated more strongly with cognitive/effort measures than with ABR metrics [9].

Hence, even though the concept of HHL has strong mechanistic support, **clinical application is still limited**. Clinicians must therefore interpret any objective measure cautiously and always in context (noise history, audiogram, OAE, speech-in-noise testing, cognitive screening).

Emerging Diagnostic Tools

This section summarizes key electrophysiological and anatomical proxies being investigated for synaptopathy detection, with representative studies.

Auditory Brainstem Response (ABR)

The ABR is a long-standing tool in auditory diagnostics. For synaptopathy, the primary focus is the amplitude (and sometimes latency) of **wave I**, which reflects the summed auditory nerve fiber activity; a smaller wave I amplitude (despite normal threshold) is hypothesized to indicate synaptic loss [49]. In animal models, synaptopathy yields clear wave I reductions independent of threshold shift [21,50]. Some human studies, such as Bramhall et al. (2022), reported smaller wave I amplitudes in high-noise-exposed groups [52]. However, many other human studies find no significant correlation between noise exposure or speech-in-noise performance and wave I amplitude [19,15]. Notably, the **wave V/I ratio** (wave V generation in the brainstem vs wave I) has been proposed as an index of central gain compensation—an elevated ratio may suggest peripheral loss compensated centrally [53,54]. ABRs recorded in background noise or with high-level clicks may increase sensitivity, but normative databases are lacking [51].

Envelope-Following and Frequency-Following Responses (EFR/FFR)

EFR/FFR measure sustained neural phase-locking to sound envelopes or frequency components. Because low-SR fibers contribute to encoding in noise and high-level signals, decline in these fibers should reduce EFR amplitude [55]. Zink et al. (2024) conducted a cross-species study (humans and gerbils) and found middle-aged humans had significantly reduced EFR strength compared to younger subjects, paralleling gerbil synaptopathy histology [56]. Le Prell et al. (2023) reported strong correlations between EFR harmonic amplitude and speech-in-noise performance in normal-hearing adults [57]. Still, multiple human studies have failed to show reliable EFR deficits in noise-exposed vs control groups when using standard sinusoidal modulations [58,11]. Stimulus parameters (modulation rate, frequency band, level) appear critical. Derived-band FFR or high-modulation-rate EFR may enhance sensitivity.

Middle-Ear Muscle Reflex (MEMR)

The acoustic middle-ear muscle reflex (stapedius/dilator) is triggered by synchronous high-level ANF input. Because low-SR fibers are key to reflex activation, synaptopathy should elevate MEMR thresholds or reduce reflex magnitude. Animal models confirm this [59]. In humans, Mepani et al. (2020) measured wideband MEMR thresholds and found elevated thresholds and reduced reflex growth in noise-exposed normal-hearing adults; MEMR strength correlated with word recognition in noise [60]. More recently, a

2023 study of noise-exposed workers (85 dB A for ≥ 1 yr) showed similar reductions in MEMR strength but not threshold [6]. MEMR thus emerges as a promising non-invasive screening metric, though normative values and stimulus protocol standardization remain to be established [61].

Electrocochleography (ECochG)

ECochG records cochlear potentials: the summing potential (SP, from hair cells) and action potential (AP, from auditory nerve). In synaptopathy, the AP (neural) amplitude should decrease relative to SP (hair-cell) amplitude, so an increased **SP/AP ratio** is expected [62]. For example, a case-control study (2024) in Egypt found that the SP/AP ratio and ABR wave I/V ratio differed significantly between noise-exposed complaint cases and controls; the best discriminator was the SP/AP ratio (AUC highest) [4]. Yuan et al. (2021) found that AP amplitudes but not SP differed between noise-exposed and control groups [63]. ECochG thus holds potential but is more invasive (requires specialized electrodes) and is subject to electrode placement/middle-ear status effects.

Extended High-Frequency Audiometry and Otoacoustic Emissions

While not strictly synaptopathy measures, ultrahigh-frequency (UHF) audiometry (e.g., 9–16 kHz) and distortion-product OAEs have been proposed as adjuncts: subtle hair-cell injury may accompany synaptopathy, and UHF thresholds may detect early OHC damage [0]. Some studies suggest UHF thresholds correlate with lifetime noise exposure and speech-in-noise difficulties [0]. A systematic review concluded these tests may help identify mixed (hair-cell + synaptic) injury [0].

Multimodal Test Batteries & Behavioural Correlates

Because any single metric has limited specificity/sensitivity, many authors now advocate combining objective metrics (ABR, EFR, MEMR, ECochG) with behavioural tests (speech-in-noise, temporal fine structure, gap detection) and self-report (listening effort scales) [48]. For example, Ponsot (2024) used a cross-species EFR + pupillometry paradigm in humans and gerbils and found that reduced EFR strength and increased listening-effort (indexed by pupil dilation) each predicted speech-in-noise performance beyond audiometric thresholds [20].

Clinical Implications

For audiologists and neuroscience researchers, HHL underscores that **normal audiogram = normal hearing** is no longer tenable. Patients may present with measurable suprathreshold deficits, listening fatigue, tinnitus, and speech-in-noise difficulties despite thresholds ≤ 20 –25 dB HL [65]. Recognizing HHL reframes diagnostic practice: clinicians should ask about noise history (even recreational), ototoxic exposures, listening effort, tinnitus/hyperacusis, and perform speech-in-noise or effort-based tests.

Although no FDA-approved treatments exist for synaptopathy per se, several clinical implications follow:

- **Preventive counselling:** Emphasize hearing protection even when thresholds are good; moderate noise exposures may trigger synaptopathy [66].
- **Supplemental diagnostics:** Incorporate objective suprathreshold measures (e.g., MEMR, ABR/EFR) when patients report “normal hearing but difficulty” in noise.
- **Rehabilitation strategy:** For HHL, amplification (hearing aids) may be less appropriate compared to strategies that improve signal-to-noise ratio (directional microphones, remote mics), auditory-training programs focusing on temporal/envelope cues, and cognitive/effort-reduction interventions [67].
- **Monitoring for progression:** Patients with documented synaptopathy markers may be at elevated risk

of future threshold shifts or other auditory pathologies; regular follow-up is prudent [68].

- **Research participation:** Audiologists should consider referring eligible patients for research protocols investigating synaptopathy or future therapies.

In short, HHL demands a shift from purely threshold-based diagnostics to **neural integrity-based** assessment and a more nuanced approach to “normal hearing”.

Future Directions

Continuing research in HHL aims to refine diagnostics, develop standardized criteria, explore therapies, and understand broader implications (e.g., cognitive decline, quality of life).

Standardisation & Normative Databases: Move toward standard protocols for ABR wave I amplitude, EFR modulation paradigms, MEMR strength/growth, ECoChG SP/AP ratios; build large normative databases stratified by age, sex, noise-exposure history, head size [69]. A recent systematic review (2023) emphasised that heterogeneity in protocols contributes to conflicting findings [48].

Longitudinal Cohort Studies: Essential to determine whether early synaptopathy biomarkers predict later threshold elevation, speech-in-noise decline, or cognitive impairment. One open question remains whether synaptopathy is a marker for broader neurodegeneration (e.g., dementia links) [20].

Stimulus Optimization and Analytics: Advances in stimulus design (e.g., derived-band FFR, high-level EFR in noise, broadband MEMR growth), and machine-learning analysis of waveform features, promise enhanced sensitivity [74]. Computational auditory-nerve models also guide better diagnostics.

Therapeutic Interventions: Animal studies show promise for **synapse regeneration**. For example, Seist et al. (2020) reported bisphosphonate treatment in mice after noise exposure induced IHC–ANF synapse regrowth and improved ABR/behavioral outcomes [72]. Gene-therapy, neurotrophin delivery, and small-molecule synaptopathy treatments are in preclinical development. Clinical trials in humans may follow.

Integration with Cognitive and Central Auditory Research: As Ponsot (2024) suggests, synaptopathy interacts with central listening-effort and cognitive factors; investigations into cortical compensatory changes, listening-fatigue biomarkers (e.g., pupillometry, EEG), and quality-of-life endpoints are crucial [20]. Further, understanding how cochlear synaptopathy relates to tinnitus, hyperacusis, and vestibular disorders remains an active area [26].

Global and Resource-Limited Settings: In places such as India (relevant to many audiologists), developing affordable test batteries (e.g., smartphone-based EFR, MEMR with simple reflex equipment) is vital to translate HHL diagnostics culturally and economically [68].

Conclusion

Hidden hearing loss and cochlear synaptopathy represent a paradigm shift in audiology: hearing impairment begins not only with hair-cell death and thresholds but may first occur at the level of synapses between IHCs and ANFs. While standard audiometry misses this early neural damage, converging evidence from histopathology, animal and human physiology, and behavioural studies confirms the existence and functional relevance of synaptopathy. For the audiologist and neuroscience researcher, this means moving toward assessment of **neural integrity**, via electrophysiological, reflexive, and behavioural measures, and recognizing that normal thresholds do not guarantee normal suprathreshold auditory performance.

Although no definitive clinical test or therapy yet exists for HHL in individual patients, the agenda is clear: (1) refine and standardize diagnostics (ABR, EFR, MEMR, ECoChG); (2) combine objective metrics with

behavioural and self-report measures; (3) monitor at-risk patients proactively; and (4) support ongoing translational research toward synaptic regeneration and neuro-protective strategies. As the field matures, what is currently “hidden” may become part of routine audiological assessment and early intervention.

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