THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 14 Issue 4

RESEARCH ARTICLE

# Cochlear Synaptopathy: Translational Evidence from Animal Models to Human Electrophysiological Correlates

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**PUBLISHED**
30 April 2026

**CITATION**
Kaf, WA., 2026. Cochlear Synaptopathy: Translational Evidence from Animal Models to Human Electrophysiological Correlates. Medical Research Archives, [online] 14(4).

**ISSN**
2375-1924

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## ABSTRACT

**Background:** Cochlear synaptopathy is defined as the loss of synapses between inner hair cells and auditory nerve fibers. It is well established in animal models following noise exposure and aging. In humans, direct histopathologic confirmation is not feasible; therefore, synaptopathy must be inferred from electrophysiologic and behavioral proxies, contributing to variability in findings across populations.

**Objective:** To synthesize translational evidence for cochlear synaptopathy and to evaluate the validity of electrophysiologic markers, including auditory brainstem responses, electrocochleography, envelope following responses, and middle-ear muscle reflex measures.

**Methods:** A PRISMA-informed narrative review of peer-reviewed studies indexed in MEDLINE, Scopus, and Embase was conducted. Animal, human temporal bone, and human in vivo investigations were organized thematically and tabulated to compare exposure categories, electrophysiologic measures, and clinical outcomes.

**Results:** Animal and temporal bone studies consistently demonstrate synaptic loss accompanied by reduced suprathreshold neural output despite preserved thresholds. Human findings are more heterogeneous. High-risk groups, including individuals with military or occupational noise exposure and older adults, frequently show reduced neural responses as signs of cochlear synaptopathy, whereas younger normal-hearing cohorts often show null results unless stress-test paradigms or complex electrophysiologic batteries are employed.

**Conclusion:** Cochlear synaptopathy is a biologically established neural lesion in animals but remains a probabilistic diagnosis in humans. Convergent abnormalities across multiple electrophysiologic measures enhance detection relative to single metrics and may inform future clinical trials targeting synaptic repair.

**Keywords:** Cochlear synaptopathy; Hidden hearing loss; Noise exposure; Aging; Suprathreshold auditory dysfunction; Auditory brainstem response; Electrocochleography; Envelope following response; Middle ear reflex

## Abbreviations List

ABR — auditory brainstem response
ANF — auditory nerve fiber
ANFs — auditory nerve fibers
AP — action potential
ART — acoustic reflex threshold
DPOAE — distortion product otoacoustic emission
ECochG — electrocochleography
EFR — envelope following response
IHC — inner hair cell
MEMR — middle ear muscle reflex
MOC — medial olivocochlear reflex
OAE — otoacoustic emission
OHC — outer hair cell
SP — summating potential
SP/AP — summating potential to action potential ratio
SPiN — speech in noise
TM — tympanic membrane

## Introduction

Patients frequently report difficulty understanding speech in noise, tinnitus, or abnormal sound tolerance despite normal audiometric thresholds. These discrepancies highlight limitations of the traditional model of acquired sensorineural hearing loss, which attributed symptoms primarily to sensory hair cell damage and considered auditory nerve degeneration a secondary consequence. Over the past two decades, evidence has challenged this framework by demonstrating that synapses between inner hair cells (IHC) and type I auditory nerve fibers (ANFs) are particularly vulnerable to moderate noise exposure and aging. This pathology, termed cochlear synaptopathy, can occur without permanent threshold elevation or overt hair cell loss and therefore remains undetected by conventional audiometry.[1,2]

Animal studies show that exposures producing only temporary threshold shifts can nevertheless cause permanent loss of ribbon synapses and postsynaptic terminals.[1,3] These neural changes may precede and accelerate age related cochlear degeneration.[2,3] Electrophysiologic recordings further demonstrate selective vulnerability of low- spontaneous-rate (low-SR) ANFs, which encode suprathreshold sound levels and temporal envelope information, whereas high-SR ANFs that determine thresholds are relatively preserved.[4,5] This selective neural injury provides a mechanistic explanation for degraded temporal precision and suprathreshold coding despite normal audiometric thresholds and has been proposed as a biological basis for the clinical phenotype often termed hidden hearing loss, including speech in noise difficulty, tinnitus, and hyperacusis.[6,7, 8]

Consistent electrophysiologic signatures of synaptopathy have been documented in animals, including reduced compound action potential amplitudes, reduced auditory brainstem response (ABR) wave I amplitude, degraded envelope following responses (EFR), and weakened middle ear reflexes.[7,9,10] These neural deficits persist after recovery of thresholds and otoacoustic emissions (OAEs), demonstrating a dissociation between sensory cell integrity and neural output. [1,9] Confirmation in nonhuman primates further strengthens the biological and translational relevance of this lesion.[10]

Translation to humans remains challenging because cochlear histopathology cannot be assessed in vivo. Evidence therefore derives from two complementary sources. Human temporal bone studies demonstrate primary neural degeneration with aging and greater neural loss in noise-exposed individuals, associated with poorer speech recognition beyond what audiometric thresholds predict.[11] In parallel, investigators have evaluated electrophysiologic proxies including ABR amplitude and latency measures, electrocochleography (ECochG) action potential metrics, EFR, and middle ear reflex growth.[7,12-14]

Human findings, however, remain inconsistent. Some high risk populations such as military or occupational noise exposure cohorts demonstrate reduced suprathreshold neural metrics,[13,15,16] whereas studies of young normal-hearing listeners frequently report null associations between noise history and electrophysiologic outcomes.[17-19] Methodological factors such as exposure characterization, recording paradigms, and stress paradigms appear to influence detectability, with rate stress ECochG and combined measures improving sensitivity.[20-22] Similarly, associations between synaptopathy and tinnitus or speech in noise deficits remain variable across cohorts.[6,23 24]

Collectively, the literature demonstrates a translational asymmetry: cochlear synaptopathy is a histopathologically confirmed neural lesion in animals but a probabilistic construct in humans inferred from convergent electrophysiologic evidence. Clarifying which biomarkers meaningfully reflect neural injury and under what conditions they are interpretable is therefore essential for clinical translation. The objective of this narrative review is to integrate animal, temporal bone, and human data within a translational framework, evaluate electrophysiologic indicators of cochlear synaptopathy, and define criteria under which synaptopathy may be considered definite, probable, or possible in clinical populations.

## Methods

### STUDY DESIGN

To address the translational gap identified above, this study was conducted as a PRISMA informed narrative synthesis of indexed, peer-reviewed literature examining cochlear synaptopathy and hidden hearing loss. The aim was to integrate evidence across animal histologic and physiological investigations and human clinical studies, with emphasis on electrophysiologic biomarkers of neural dysfunction.

### SEARCH STRATEGY

A comprehensive literature search was performed using MEDLINE via PubMed, Scopus, and Embase. Searches were conducted without restriction on publication year and were limited to English language articles. Boolean strategies were adapted to each database to capture both mechanistic and clinical evidence related to cochlear synaptopathy and its electrophysiologic correlates.

The primary search string was: ("cochlear synaptopathy" OR "hidden hearing loss") AND ("auditory nerve" OR "auditory brainstem response" OR ABR OR electrocochleography OR ECochG OR "envelope following response" OR EFR OR "middle ear muscle reflex" OR MEMR). Supplementary searches included: ("noise induced synaptopathy" OR "age related synaptopathy") AND (ABR OR ECochG OR EFR OR MEMR) Reference lists of relevant reviews and seminal experimental studies were manually screened to identify additional eligible articles.

SCREENING AND ELIGIBILITY

Combined electronic and manual searches yielded several hundred records. After removal of duplicates, titles and abstracts were screened for relevance. Approximately 90 to 120 full text articles were reviewed in detail. From these, a curated subset of approximately 40 to 60 studies was selected for qualitative synthesis based on direct relevance to cochlear synaptopathy and translational applicability.

Because of substantial heterogeneity in exposure characterization, experimental paradigms, and outcome measures, quantitative meta-analysis was not appropriate. Instead, studies were synthesized thematically according to predefined eligibility criteria.

INCLUSION CRITERIA

- Peer-reviewed, indexed journal articles
- Animal or human studies investigating IHC-ANF synapse loss or neural degeneration
- Histopathologic or electrophysiologic investigations
- Use of electrophysiological measures relevant to synaptopathy including ABR, ECochG, EFR, FFR, and/or MEMR
- Populations involving noise exposure, aging, tinnitus, hyperacusis, or speech-in-noise difficulty

EXCLUSION CRITERIA

- Non peer-reviewed or non-indexed publications
- Editorials, commentaries, or opinion articles
- Studies without neural or synaptic relevance

DATA SYNTHESIS

Eligible studies were grouped thematically and summarized in Table 1 for animal investigations and Table 2 for human studies. Findings were synthesized qualitatively with emphasis on translational convergence between histopathologic evidence and electrophysiologic biomarkers.

## Results

Following the thematic classification described in the Methods, studies were grouped into animal histopathologic models and human electrophysiologic cohorts to assess convergence between histopathology and physiological biomarkers of cochlear synaptopathy.

A) ANIMAL EVIDENCE OF COCHLEAR SYNAPTOPATHY

Animal models provide direct evidence of cochlear synaptopathy and establish the electrophysiological basis for interpreting human findings. Across diverse animal models (mouse, guinea pig, rat, gerbil, non-human primate), convergent evidence shows that moderate noise exposure and aging consistently produce cochlear synaptopathy—loss of IHC ribbon synaptic connection with ANFs, while audiometric thresholds and outer hair cells (OHC) remain near-normal. This neural deafferentation explains reduced suprathreshold neural output and degraded temporal, binaural coding, despite preserved sensory cell integrity and normal hearing thresholds.[1,2]

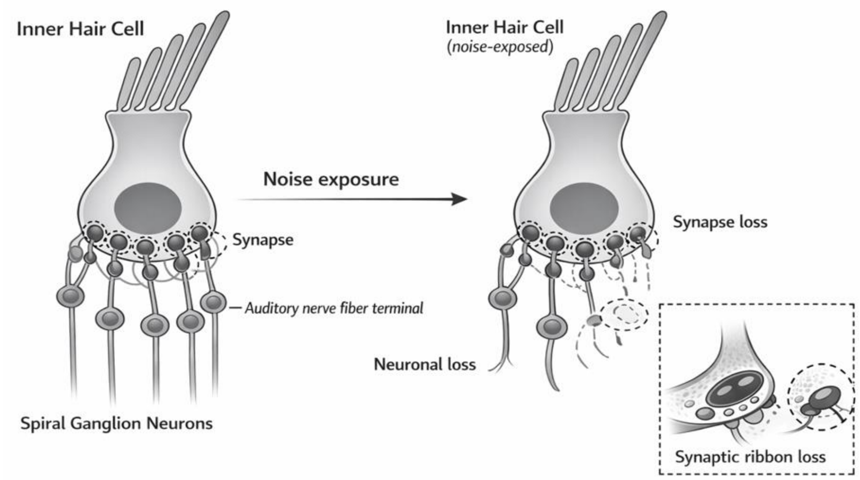

**Figure 1. Histopathologic schematic of cochlear synaptopathy in an animal model.**
**Left Panel,** normal inner hair cell (IHC) with intact ribbon synapses (black circles) and auditory nerve fiber (ANF) terminals contacting the basolateral pole. **Right Panel,** after noise exposure, ribbon synapse loss, ANF terminal retraction, and degeneration of peripheral spiral ganglion processes are evident. The inset highlights presynaptic ribbon loss at the IHC–ANF junction, the primary lesion of cochlear synaptopathy. This neural deafferentation reduces suprathreshold neural responses despite normal hair cell morphology and thresholds (“hidden hearing loss”), consistent with histopathology from noise-exposed animal models.

As illustrated in Figure 1, noise exposure produces a selective pattern of primary neural injury at the IHC ribbon synapses. Under normal conditions (left panel), the IHC displays a full complement of presynaptic ribbons and intact ANF terminals. After synaptopathic noise exposure (right panel), the schematic illustrates loss of IHC ribbon synapses, retraction of ANF terminals, and early degeneration of spiral ganglion neuron peripheral processes, reflecting the sequence of afferent disconnection observed in experimental models. The inset further depicts presynaptic ribbon loss at the IHC synapse, a hallmark of cochlear synaptopathy. The synaptic disconnection precedes any overt hair cell damage and represents the initiating lesion in hidden hearing loss.

As summarized in Table 1 and illustrated in Figure 1, suprathreshold neural responses remain reduced even after recovery of hearing thresholds and distortion-product otoacoustic emissions (DPOAEs).[1-3] Findings also show that hair cell loss is minimal with only temporary threshold shifts at exposure levels that produce synaptic injury and permanent synaptic loss. These findings indicate that permanent threshold shift requires greater damage than neural deafferentation. Live imaging corroborates that ribbons become enlarged, mobile, and unanchored immediately after exposure, indicating rapid presynaptic disruption that precedes overt hair cell damage.[1] Selective vulnerability of low-SR, high threshold ANFs explains preserved thresholds despite degraded neural coding.[2,3] Evidence in rhesus macaques demonstrates that this mechanism generalizes beyond rodents, with synapse loss of approximately 12 to 27 percent after temporary threshold shift and 50 to 75 percent after permanent threshold shift.[1,3,4]

Rodent studies consistently demonstrate that synaptopathy can be reliably induced using octave-band noise centered between 8 and 16 kHz at intensities of approximately 94–109 dB SPL, producing robust and reproducible ribbon-synapse loss. Primate models require higher levels to produce permanent threshold shifts but still show synaptic loss with partial threshold recovery. Blast exposure produces combined peripheral and central injury patterns. Although the magnitude and time course vary according to exposure spectrum, level, duration, strain, and assay method, synapse loss occurs rapidly within minutes to hours and shows minimal long-term recovery.[10]

Electrophysiologic measures closely parallel histologic findings. Temporary threshold shifts occur immediately after exposure, followed by persistent reductions in suprathreshold neural output even after recovery of thresholds and OAEs. Reduced ABR wave I amplitude correlates with synapse counts and possibly serves as a marker of neural injury.[1-3] Invasive round window ECochG decomposition separates hair cell and neural contributions and detects neural loss in animal models; applied to human surgical cohorts, the neural component often resembles partial synaptopathy, indicating viable hair cells that lack afferent connections (Haggerty et al., 2023). Efferent, medial olivocochlear (MOC) reflex provides sensitive readouts: in mice with noise-induced neuropathy, the wideband middle ear muscle reflex (MEMR) shows elevated thresholds and reduced growth, often outperforming suprathreshold ABR amplitude as a synaptopathy correlate.[20,25]

With aging, synaptic loss is detectable before age-related cochlear hair cell loss or threshold elevation and is often tonotopically biased. In gerbils, quiet-aged ears show approximately 20% synapse loss overall, with a preferential loss on the modiolar (typically low-SR) side of IHCs in the basal, high-frequency region, supporting a fiber-class vulnerability critical for listening in noise and gap detection skills.[2,3,26,27] A study examining the interaction between early noise exposure and aging found that mice exposed to noise causing a moderate permanent threshold shift later developed delayed spiral ganglion neuron loss over months to years, despite no loss of OHCs or IHCs.[28] Follow-up synaptic analysis indicated early damage at the IHC–ANF synapses, suggesting that primary synaptopathy drives the later age-related neural degeneration.[29,30]

Importantly, synaptic regeneration in vivo is feasible through two complementary approaches: (a) post-exposure delivery of neurotrophin-3 (NT-3) protein to the round window which supports spiral ganglion neuron survival and synaptic maintenance at the IHC synapse, and (b) overexpression of the Ntf3 gene, which encodes NT-3 protein, leading to increased synaptic counts. Both approaches restore ribbon synapse counts and improve suprathreshold ABRs, demonstrating a therapeutic window for repair.[9]

These histopathologic and electrophysiologic findings establish cochlear synaptopathy as a definitive neural lesion in animal models, characterized by reduced suprathreshold neural output despite recovery of thresholds and OAEs. The translational question that follows is whether comparable suprathreshold neural signatures can be identified in humans, where direct histopathologic confirmation is not feasible.

**Table 1. Animal evidence of cochlear synaptopathy**

| Author (Year) | Species | Noise/Aging | Measures | Histopathology | Electrophysiology |
|---|---|---|---|---|---|
| ***Noise-induced model*** | | | | | |
| Bakay et al. (2018)[31] | Mouse | Single loud-noise episode (HHL model) vs control | ABR, IC recordings | IHC synapse loss in 22–45 kHz region; OHC loss ≤7% (minimal) | ABR: Wave I ↓; central adaptation to fluctuating sound environments ↓ (IC recordings) |
| Valero et al. (2018)[20] | Mouse | Noise: octave band 8–16kHz | MEMR, ABR, DPOAE | 4–50% synapse loss | Wave-I attenuated |
| Mehraei et al. (2016)[13] | Mouse | Noise: neuropathic vs control | Masked ABR, DPOAE | ~44% ribbon loss | Wave I latency shift in noise = temporal coding degradation |
| Valero et al. (2016)[25] | Mouse (mixed strain) | Neuropathic noise exposure | Wideband MEMR paradigm | Cochlear synaptopathy present in exposed ears | Wideband MEMR: threshold ↑; max amplitude ↓ |

| Author (Year) | Species | Noise/Aging | Measures | Histopathology | Electrophysiology |
|---|---|---|---|---|---|
| Fernandez et al. (2015)[3] | Mouse (CBA/CaJ) | Noise: 8–16kHz OBN; synaptopathic vs PTS paradigms | ABR, DPOAE | IHC synapses ↓; hair cells preserved in synaptopathy-only; greater damage with PTS | Wave-I ↓; thresholds may recover; DPOAE→ (no change) in synaptopathic-only conditions |
| Hickox & Liberman (2014)[32] | Mouse | Noise-induced neuropathy | PPI, ABR | Primary neural degeneration | Central gain increased |
| Maison et al. (2013)[33] | Mouse | Moderate noise + OCB cut | ABR, DPOAE | ~40% synapse loss | ABR amplitude declines |
| Kujawa & Liberman (2009)[1] | Mouse (CBA/CaJ) | Noise: 8–16kHz 100dB 2h | ABR, DPOAE | IHC synapse loss | Wave-I reduced |
| Benson et al. (2024)[34] | Guinea pig | Noise (moderate exposure): binaural deficit model | Binaural metrics | Ribbon loss | Binaural deficits |
| Xia et al. (2022)[35] | Guinea pig | Intermittent noise | ABR/EFR | Synaptopathy minimal threshold change | Temporal deficits |
| Furman et al. (2013)[4] | Guinea pig | Noise: 4–8kHz 106dB 2h | Single fiber, ABR, DPOAE | ~30% synapse loss | Low-SR loss |
| Valero et al. (2017)[10] | Rhesus macaque | Noise: 2kHz NB 4h TTS/PTS | ABR, OAE | 12–27% TTS; 50–75% PTS | Wave-I reduced |
| Haggerty et al. (2023)[36] | Gerbil + human | Noise + neurotoxin | ECochG | Neural contribution loss | Synaptopathy detected |
| ***Noise exposure and treatment*** | | | | | |
| Lin et al. (2024)[38] | Guinea pig male, pigmented; C-PC treatment vs saline control | Noise: 24–32 kHz tonebursts; synaptopathic; pharmacologic rescue | ABR, ICAM-1, ROS | Treated group: ↑ IHC ribbons; ↓ ICAM-1 ↓ ROS/NOX4; | Treated group: Wave-I ↑ |
| Suzuki et al. (2016)[39] | Guinea pig Noise + NT-3 vs noise + vehicle; controls | Noise-induced synaptopathy; Noise + NT-3 via round window | ABR | Ribbon synapses: noise ↓; NT-3 regeneration ↑ | ABR Wave I: noise ↓; NT-3 recovery ↑ vs vehicle |
| Wan et al. (2014)[9] | Mouse | Acoustic trauma: Ntf3 overexpression vs control (post-trauma) | Auditory responses + Ntf3 | Ribbon synapses: regeneration ↑ with Ntf3 | Auditory responses: recovery ↑ with Ntf3 |
| ***Aging model*** | | | | | |
| Bovee et al. (2024)[26] | Gerbil (aged) | Aging | Immunolabeling: apical/ middle/basal | 20% ribbon loss | Basal selective loss |
| Dorje et al. (2024)[37] | Mouse (CBA/J) | Aging lifespan study | Ribbon vs MOC-OHC | Afferent declines earlier | Afferent vulnerable |
| Kurioka & Mizutari (2024)[27] | Mouse (CBA/J; 1–12 months) | Aging: 1,6,12mo | ABR, DPOAE, PPI | GAD65↓; PV+↓ | Gap detection degraded |
| Sergeyenko et al. (2013)[2] | Mouse (CBA/CaJ) | Aging 4–144wks | DPOAE, ABR | Progressive ribbon loss | Neural declines early |
| Mohrle et al. (2016)[28] | Rat | Aging ± trauma | ABR, behavior | Age-dependent changes: ribbons loss more in young than old rats, more in midbasal and basal turns of the cochlea. | Wave-I ↓<br>Compensation fails in old |

**Abbreviation:** ABR (Auditory Brainstem Response), AMPA/GluA2 (postsynaptic glutamate receptor), ANF (auditory nerve fiber), A1 (primary auditory cortex), ASR (acoustic startle response), C-PC (C-phycocyanin), CAP (compound action potential), CtBP2 (presynaptic ribbon marker), DPOAE (distortion-product otoacoustic emission), ECochG (electrocochleography), EFR (envelope-following response), GAD65 (glutamic acid decarboxylase-65), GPIAS (gap-prepulse inhibition), IHC (inner hair cell), ICAM-1 (intercellular adhesion molecule-1), KO/WT (knockout/wild-type), MEMR (middle-ear muscle reflex), MOC (medial olivocochlear system), NB (narrow-band noise), NOX4 (NADPH oxidase-4), OHC (outer hair cell), OCB (olivocochlear bundle), PPI (prepulse inhibition), PTS (permanent threshold shift), PV+ (parvalbumin-positive neuron), ROS (reactive oxygen species), RW (round window), SGN (spiral ganglion neuron), SR (spontaneous rate), SPL (sound pressure level), TTS (temporary threshold shift), VGLUT1 (vesicular glutamate transporter-1).

## B) HUMAN ELECTROPHYSIOLOGIC EVIDENCE

In the absence of in-vivo histopathology, human investigations rely on electrophysiologic and behavioral proxies to infer cochlear synaptopathy.

Table 2 synthesizes empirical evidences across human studies investigating behavioral and electrophysiologic correlates of cochlear synaptopathy across exposure categories, including recreational noise, occupational and military noise exposure, tinnitus, and aging. As in the animal literature, findings cluster around suprathreshold neural dysfunction rather than threshold elevation.

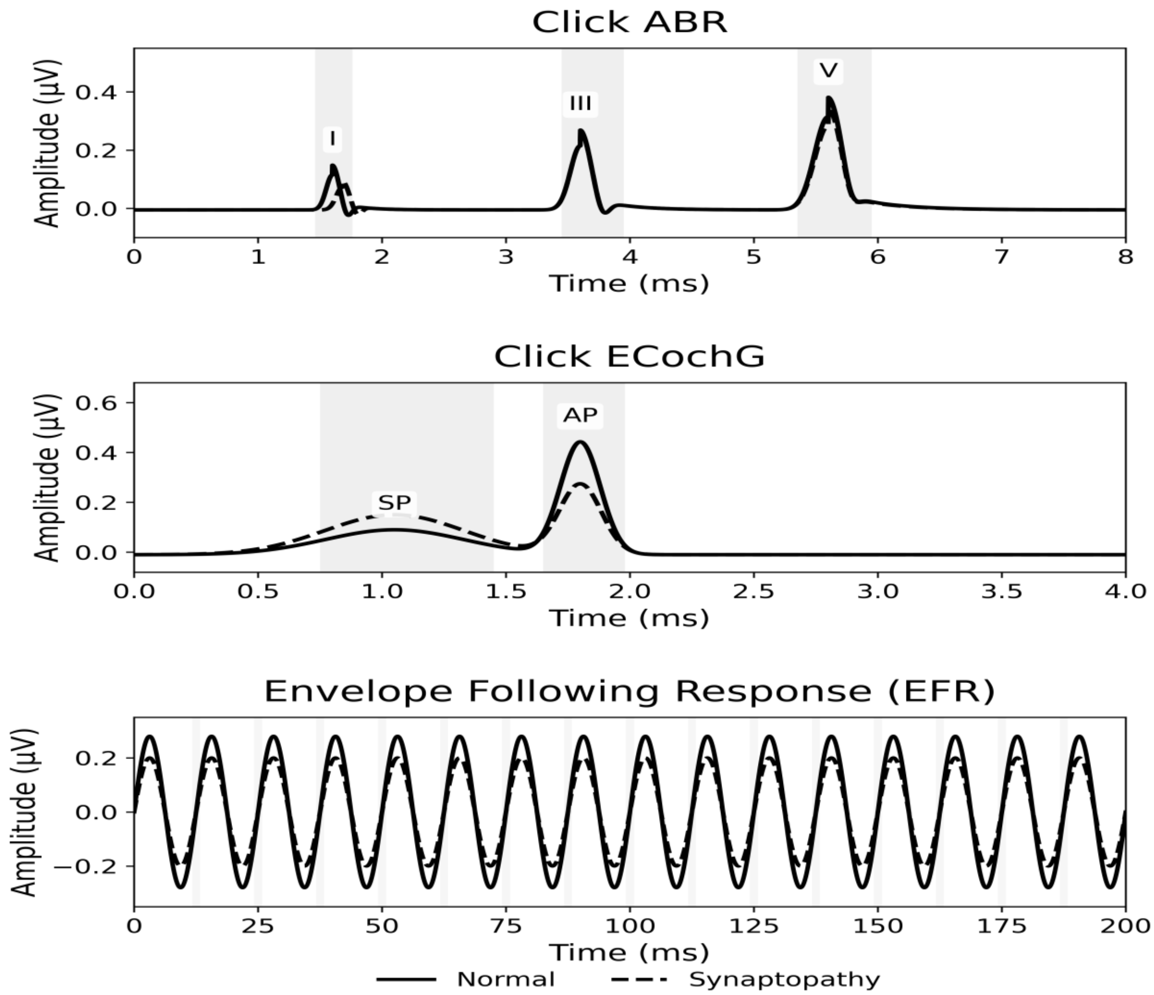

**Figure 2. Schematic *electrophysiologic markers of cochlear synaptopathy.***
**Top Panel:** Click auditory brainstem response (ABR) showing reduced wave I amplitude with relative preservation of waves III and V, consistent with reduced auditory nerve output and central gain compensation. **Middle Panel:** Electrocochleography (ECochG) demonstrating reduced action potential (AP) amplitude with enlarged summating potential (SP), resulting in increased SP/AP amplitude and area ratios. **Bottom Panel:** Envelope following response (EFR; 80-Hz modulation) showing reduced neural synchrony in cochlear synaptopathy. Solid traces denote normal responses; dashed traces denote synaptopathy.

Figure 2 summarizes representative electrophysiologic response patterns associated with cochlear synaptopathy. The click ABR (Panel A) demonstrates reduced wave I amplitude with relatively preserved waves III and V, consistent with reduced auditory nerve output and relative preservation of more central generators. The click ECochG response (Panel B) shows reduced action potential (AP) amplitude accompanied by an abnormally large summating potential (SP), resulting in elevated SP/AP amplitude and area ratios in cochlear synaptopathy. The EFR (Panel C) displays reduced response magnitude in cochlear synaptopathy, consistent with decreased neural synchrony. These electrophysiologic patterns reflect reduced synaptic integrity at the IHC–ANF interface, leading to diminished neural output and impaired temporal coding despite preserved OHC function and normal audiometric thresholds.

Across human cohorts, electrophysiologic patterns are systematic but heterogeneous. Abnormalities are most consistently observed in well-characterized, high-risk populations, including military veterans, occupational noise exposure groups, and older adults. These cohorts demonstrate reduced suprathreshold neural output, reflected by smaller ABR wave I amplitudes, approximately 0.21 µV compared with 0.34 µV in controls[16,21], elevated SP/AP ratios on ECochG[12,22], reduced EFR magnitude or slope[15], and weakened MEMR responses with reductions of approximately 30% to 40% across modulation conditions.[16,21,25] Aging cohorts further show reduced neural growth functions and poorer speech in noise performance despite preserved thresholds, aligning with human temporal bone evidence of neural fiber loss.[11] Human temporal bone studies provide indirect confirmation of neural loss, demonstrating degeneration of ANFs associated with poorer word recognition at comparable thresholds.[40]

In contrast, studies of young adults with normal audiograms and primarily self-reported recreational noise exposure frequently report null or small associations between exposure history and ABR, EFR, or MEMR measures.[17-19] This divergence suggests that exposure characterization, central compensation, and measurement sensitivity strongly influence detectability. When neural responses are stressed or recorded near the cochlea, measurable differences emerge. Kaf et al. (2022) reported reduced ABR wave I amplitude at fast stimulation rates in listeners with higher real-world music exposure, whereas slow rate responses were similar between groups; the same cohort demonstrated increased ECochG SP/AP ratios.[22] Liberman et al. (2016) likewise reported elevated SP/AP ratios in high-risk listeners despite normal thresholds.[12]

**Table 2. Continued. Human markers and procedures to assess probable cochlear synaptopathy**

| Authors (Year) | Participants/Groups | Exposure/Risk | Physiologic Measures | Key Findings |
|---|---|---|---|---|
| ***Recreational / Personal Music Noise*** | | | | |
| Kaf et al (2022)[22] | 15 high-risk; 15 low-risk; age 18–26; normal hearing and OAE | Noise exposure (iPhone Health App estimate) | DPOAE (1–12 kHz); simultaneous ABR/ECochG (click 19.5, 97.7, 234.4/s) | ABR wave I reduced at fast rates in high-risk; ECochG SP/AP amplitude and area ratios increased at fast rates in high-risk |
| Bal (2021)[41] | 25 high-risk; 25 controls | Music exposure (ETDNL) | ABR; ECochG; tympanometry; matrix test | AP and wave V amplitudes reduced in high-risk; no association between ETDNL and V/I ratio; TurMatrix performance reduced in high-risk |
| Suresh & Krishnan (2021)[42] | 28 high-risk; 28 controls; normal hearing | Marching band ≥5 years vs minimal hx of loud-sound | ABR (click, BBN); DPOAE | No difference in DPOAE or wave III/V; high-risk group showed reduced wave I amplitude at moderate/high levels and enhanced V/I ratio |
| Grose, Buss, Hall (2017)[17] | 31 noise-exposed; 30 controls; age 18–35; normal hearing | Music exposure; ≥25 loud events in 1 year and ≥40 in 2 years | DPOAE I/O (0.5–8 kHz); ABR (click 7.7/s); EFR; AAC; CNC; BKB | No differences in DPOAE, EFR, AAC; wave I amplitude reduced in exposed group; no differences in CNC, BKB, audiometry |
| Stamper & Johnson (2015)[43] | 30 adults; age 19–28; normal hearing and DPOAE | Noise exposure questionnaire (NEQ) | DPOAE I/O (1, 2, 4 kHz); ABR (click and 4 kHz, 11.3/s) | Wave I amplitude decreased as noise exposure increased; no DPOAE changes |
| ***Occupational / Mixed Noise*** | | | | |
| Cildir (2022)[44] | 39 high-risk; 30 low-risk; age 18–32; normal hearing and DPOAE | "1-minute noise screen" score ≥5 | ABR (click 9.1/s); matrix test; AMDT; loudness adaptation | High-risk group showed increased V/I ratios, reduced wave I amplitude at high intensities, increased AMDT |
| Pinsonnault-Skvarenina et al (2022)[45] | 40 noise-exposed; 40 controls; normal hearing and DPOAE | Occupational exposure to 80 dBA LAeq.8h; CNE; HPD use | ABR (click 11.1/s); SPiN (BKB) | No ABR differences; SPiN worse in noise-exposed group (likely non-sensory factors) |
| Guest H (2018)[18] | 16 SPiN-impaired; 16 controls; age 18–40; normal hearing | SPiN impairment | Pure-tone thresholds; NESI; ABR; EFR | No differences in ABR wave I or V/I ratio; no association between EFR and SPiN impairment |
| Encina-Llamas (2019)[46] | 9 normal hearing; 4 mild hearing loss | Mild hearing loss | EFR; auditory nerve model | EFR slope reduced in mild hearing loss; EFR dominated by high-SR fibers |
| ***Military/Veterans*** | | | | |
| Bramhall et al (2021)[16] | 48 veterans; 31 non-veterans; age 19–35; normal hearing and DPOAE | Veteran noise exposure; LENS-Q | ABR (4 kHz, 11.1/s); EFR | Veterans showed reduced ABR wave I and reduced EFR magnitudes |
| Bramhall et al (2017)[47] | 29 veterans; 25 non-veterans; age 19–35; normal hearing | Veteran status; firearm use | ABR (3, 4, 6 kHz; 11.1/s) | Wave I amplitude reduced in high-risk group |
| ***Tinnitus (Normal Audiogram or Mixed)*** | | | | |
| Guest H (2017)[23] | 20 tinnitus; 20 controls; age 21–29; normal hearing | Noise exposure; tinnitus (TFI) | ABR (high-pass clicks); EFR | No ABR or EFR differences |
| Singer (2013)[48] | Tinnitus cohort | Noise exposure; tinnitus | ABR | IHC ribbon loss associated with tinnitus despite reduced ABR |
| Schaette & McAlpine (2011)[6] | 15 tinnitus; 18 controls; age 30–39; normal hearing | Tinnitus | ABR (click 11/s) | Wave I amplitude reduced in tinnitus group; wave V unchanged |

| Authors (Year) | Participants/Groups | Exposure/Risk | Physiologic Measures | Key Findings |
|---|---|---|---|---|
| Paul (2017)[49] | 13 tinnitus; 24 controls | Tinnitus (THQ) | AMDT; EFR | Tinnitus group showed poorer AM detection and reduced EFR |
| Wojtczak (2017)[21] | 18 tinnitus; 18 controls; mostly normal hearing | Noise-triggered tinnitus | Wideband MEMR | MEMR strength reduced in tinnitus group |
| ***Aging/Lifespan*** | | | | |
| Liberman (2016)[12] | 34 adults; age 18–41; normal hearing | Noise exposure questionnaire | Audiometry; WRS; DPOAE; ECochG | High-risk group showed elevated thresholds >8 kHz, reduced WRS in noise, increased SP/AP ratio |
| Fujihira (2024)[50] | 57 adults; age 20–68; normal hearing | Aging | ABR (single/paired clicks); WRS | Post-wave I response correlated with WRS; wave I amplitude not correlated with age |
| Schmidt (2024)[51] | 80 adults; age 18–61; normal hearing | Aging | Audiometry (0.125–16 kHz); ABR | Negative correlation between curvature and age; curvature correlated with high-frequency thresholds |
| Seo (2022)[52] | 19 ISSNHL recovery; mean age 45.7 | Recovered ISSNHL | WRS; ABR | Recovered ear showed reduced wave I amplitude; wave V unchanged |
| Carcagno & Plack (2020)[53] | 102 adults; normal hearing 0.125–2 kHz; mild 3–4 kHz | Aging | ABR; FFR | Wave I amplitude growth reduced with age; FFR unchanged |
| Garrett (2019)[54] | 23 hearing-impaired; 22 controls | Aging/hearing loss | DPOAE; EFR; ABR; EEG | Hearing-impaired group showed elevated DPOAE thresholds, reduced ABR wave V, reduced EFR |
| Guest (2019)[14] | 30 adults; mean age 24.4; normal hearing | Reliability study | ABR; EFR; MEMR; DPOAE | Excellent reliability for EFR and MEMR; wave I amplitude increased with level |
| ***Normal-Hearing / Methods / Mixed Cohorts*** | | | | |
| Hasanpour (2025)[55] | 30 NICU neonates; 30 controls | NICU status | ABR; ART; rapid-rate ABR | No differences in wave I/V amplitude, ART, or adaptation |
| Mehraei et al (2016)[13] | 23 adults; age 20–40; normal hearing | ITD detection ability | CEOAE; ITD; ABR; masked ABR | Wave I amplitude reduced; wave V latency increased in noise; steeper wave I growth curve |

**Abbreviations:** AAC, auditory change complex; ABR, auditory brainstem response; AMDT, amplitude modulation detection threshold; ART, acoustic reflex threshold; BBN, broadband noise; BKB, Bamford-Kowal-Bench; CEOAE, click-evoked otoacoustic emission (OAE); CNE, cumulative noise exposure; ECochG, coordinate response measure; DPOAE, distortion product OAE; ECochG, electrocochleography; EFR, envelope-following response; ETDNL, estimated total daily noise level; FFR, frequency-following response; HPD, hearing protection device; HINT, Hearing in Noise Test; IHC, inner hair cell; ISSNHL, idiopathic sudden sensorineural hearing loss; ITD, interaural time difference; LAeq.8h, 8-hour equivalent continuous A-weighted sound level; LENS-Q, Lifetime Exposure to Noise and Solvents Questionnaire; MEMR, middle ear muscle reflex; NESI, Noise Exposure Structured Interview; NICU, neonatal intensive care unit; SAM, sinusoidal amplitude modulation; SP/AP, summating potential/action potential ratio; SPiN, speech-in-noise; THQ, Tinnitus Handicap Questionnaire; TFI, Tinnitus Functional Index; WRS, word recognition score.Methodological design substantially shapes outcomes. Paradigms that stress neural synchrony reveal deficits more reliably than conventional protocols. Masked ABR latency shifts[13], rapid rate stimulation and near field ECochG[22], and modulation depth dependent EFR measures[15] increase sensitivity to reduced neural output. Although EFR and MEMR findings vary across laboratories due to stimulus parameters and potential central compensation[15], studies employing objective exposure classification or stress paradigms consistently show larger effect sizes. Tinnitus cohorts demonstrate additional heterogeneity and may complicate interpretation. Some studies report reduced ABR wave I amplitude consistent with central gain compensation.[6] However, subsequent studies report mixed or null proxy evidence for synaptopathy in tinnitus populations, emphasizing heterogeneity in tinnitus mechanisms and in electrophysiologic phenotypes.[23,31]

Taken together, human evidence parallels animal findings in emphasizing suprathreshold neural coding deficits. However, because histopathologic confirmation is not feasible in vivo, no single electrophysiologic metric serves as a definitive diagnostic marker. Convergent abnormalities across complementary measures in well-characterized risk populations provide the strongest evidence for probable cochlear synaptopathy in humans.

## Discussion

The objective of this PRISMA-informed narrative review is to synthesize translational evidence for cochlear synaptopathy by integrating animal histopathology with human electrophysiologic proxy findings. Together, Tables 1 and 2 reveal a consistent pattern: animal studies establish a definitive neural lesion, whereas human studies provide probabilistic inference that depends on cohort characteristics, exposure definition, and electrophysiologic methodology.

The animal literature positions IHC–ANF synapses as an early and vulnerable site of injury after noise exposure and with aging, frequently preceding hair cell loss and threshold elevation.[1-3] A coherent mechanistic picture emerges in which low-SR, high-threshold ANFs are disproportionately compromised and vulnerable, especially in basal cochlear regions with aging. These fibers encode suprathreshold neural output while at moderate to high levels and in background noise.[4,5] The modiolar-side loss observed in gerbil IHC synapses aligns with a selective depletion of low-SR channels, providing a cellular substrate for speech-in-noise complaints despite preserved thresholds.[26]

Thus, ribbon synapse loss and the disproportionate susceptibility of low-SR, high-threshold ANFs constitute the core pathology of cochlear synaptopathy. This dissociation underlies hidden hearing loss, where preserved hearing thresholds mask substantial deficits in suprathreshold encoding, timing fidelity, loudness processing, and speech understanding. This explains why conventional audiometry can miss substantial neural injury: patients (and animals) may present with normal thresholds but degraded suprathreshold neural coding, notably a smaller ABR Wave-I and other electrophysiologic markers.[1,2]

Electrophysiologic measures in animals closely reflect this pathology, including reduced ABR wave I amplitude, abnormal growth functions, attenuated EFR, and weakened wideband MEMR.[7,9,10,20] Functionally, synaptopathy compresses the neural dynamic range and compromises temporal precision. Cross-species data indicate that ABR latency shifts in noise and reduced EFR magnitude capture degraded neural synchrony[56] [13,35], whereas binaural interaction and spatial release from masking remain impaired long after threshold recovery, highlighting enduring consequences for auditory scene analysis.[34,57,58] These changes persist after recovery of thresholds and OAEs, confirming that conventional audiometry fails to capture neural injury.

Translation to humans is limited because histopathology cannot be measured in vivo, requiring reliance on proxy biomarkers such as ABR, ECochG, EFR, and MEMR growth functions. Accordingly, evidence depends on convergence across electrophysiologic measures rather than a single diagnostic indicator. The strongest support for synaptopathy appears in cohorts with substantial and well-characterized exposure, including veterans, occupational noise populations, and older adults[16,19,21], whereas young listeners with self-reported recreational exposure often show normal electrophysiology.[17,18] This translational asymmetry likely reflects differences in self-report noise exposure accuracy, lifetime noise dose, age and sex distributions, electrophysiological test protocol and measurement sensitivity, and central compensation gain. The efferent, MOC reflex appears to modulate susceptibility and measurement sensitivity. In mouse models, wideband MEMR thresholds and magnitudes are strongly affected by synaptopathy, likely reflecting the loss of high-threshold, low-SR ANFs that drive the reflex. In humans, MEMR strength relates to performance in difficult listening environments, although clinical deployment demands attention to test–retest reliability and cross-metric variance.[24,25,59,21]

Conflicting findings across human studies reflect interacting methodological and electrophysiologic factors. Studies using objective exposure estimates or well-defined, high-risk cohorts detect neural deficits more reliably than those relying on self-report history.[16,22] Electrophysiologic outcomes also depend strongly on stimulus and recording parameters, including level, polarity, click rate, masking conditions, and electrode placement. Measurement sensitivity contributes further because ABR wave I amplitude is small and susceptible to recording noise and electrode placement, making it unreliable as a stand-alone marker. Stress paradigms that challenge neural synchrony, such as masking, paired click stimulation, rapid stimulation rate, and generator proximal recordings using TM electrodes, improve detection of neural deafferentation that may not be evident under conventional electrophysiologic test protocols.[13,14,22] Clinical heterogeneity also contributes, as tinnitus and speech in noise difficulty arise from multiple mechanisms, with some cohorts showing reduced wave I amplitude consistent with central gain while others demonstrate normal electrophysiologic responses.[6,23] Central compensation may obscure peripheral neural injury in younger listeners, whereas reduced compensatory capacity with aging increases detectability.[28,53]

Across biomarkers, measures emphasizing suprathreshold neural coding align most closely with animal pathology. EFR reflects degraded temporal coding[7], MEMR growth indicates reduced afferent drive[20,21], and ECochG AP and SP/AP ratio measures using TM electrodes and fast click rates detect neural dysfunction and adaptation deficits.[22,60] Masked and fast click rate ABR paradigms similarly reveal neural adaptation deficits.[13] No single measure reliably detects synaptopathy across listeners, but convergence across complementary measures strengthens inference.

The combined evidence supports a graded classification. Histopathologic confirmation in animal or temporal bone studies represents definite synaptopathy.[11] Multiple abnormal electrophysiologic measures in high-risk cohorts indicate probable synaptopathy, whereas a single abnormal proxy or uncertain exposure history suggests possible synaptopathy.[7,14] Because threshold audiometry primarily reflects OHC integrity, clinical evaluation should incorporate suprathreshold neural measures. Bridging bench to bedside for a practical translational battery includes ECochG measures with rate stress, suprathreshold ABR with masking noise and fast stimulation rate, EFR modulation functions, and wideband MEMR growth.[22,36] Although the use of round window ECochG recording in humans is invasive, it can isolate neural contributions and reveal orphaned hair cells. This multimodal approach mirrors the animal lesion, improves sensitivity in high-risk populations, and reduces false negative results. Given the inter-measure dissociations seen in healthy young volunteers, combining assays is prudent for robust inference.[36]

Therapeutic approaches aimed at repairing or stabilizing cochlear synapses continue to show meaningful promise. In noise-exposed animal models, round window delivery of neurotrophin-3 (NT-3) protein and Ntf3 gene overexpression have been shown to restore IHC–ANF synapses and improve ABR Wave-I amplitudes, supporting the feasibility of post-injury synaptic rescue and the translational potential of transtympanic delivery. However, overexpression strategies may have limitations under high-level stimulation, and recent work demonstrating preserved presynaptic exocytosis despite substantial ribbon loss underscores regional variability in vulnerability and the importance of timing when targeting synaptic repair.[39,61] Pharmacologic data further support synaptic modifiability. In guinea pigs exposed to 118 dB SPL noise, intracochlear administration of 5 µg/mL C-phycocyanin (C-PC) increased IHC ribbon counts, IHC–ANF synapse numbers, and ABR wave-I amplitudes relative to saline controls, effects attributed to suppression of $H_2O_2$-induced oxidative stress and cytotoxicity.[38] These findings demonstrate that cochlear synaptopathy is amenable to biological intervention and provide a rationale for developing therapeutics that target oxidative stress, synaptic preservation, and post-traumatic synaptic repair.

Overall, animal studies demonstrate cochlear synaptopathy as a primary neural lesion that reduces suprathreshold coding while sparing thresholds. Preferential vulnerability of low-SR, high threshold ANFs explains this dissociation.[4,5] Because these fibers encode sound in noise and at moderate to high levels, their loss impairs temporal precision, loudness growth, and speech perception without elevating pure tone thresholds, often termed hidden hearing loss. Clinically, this dysfunction may contribute to difficulty understanding speech in noise, tinnitus, hyperacusis, and reduced neural synchrony despite a normal audiogram, linking synaptic loss to the perceptual and electrophysiologic features of cochlear synaptopathy. In humans, evidence remains probabilistic because of methodological limitations and biologic variability. Interpretation therefore requires convergence across electrophysiologic markers and exposure risk rather than any single test. Accordingly, cochlear synaptopathy in humans should be viewed not as a binary diagnosis but as a spectrum of neural dysfunction, most reliably detected when multiple electrophysiologic measures align with well-characterized exposure risk.

In sum, animal studies converge on a model in which cochlear synaptopathy is a primary neural lesion of “hidden” hearing loss, with measurable consequences for temporal and spatial processing and actionable opportunities for repair. This evidence base strongly motivates diagnostic batteries that integrate ECochG at fast stimulation rate, ABR timing (in noise), EFRs, wideband MEMR, alongside emerging synapse-targeted therapeutics, to close the translational gap from laboratory to clinic.[1]

## Conclusion

Animal research demonstrates that cochlear synaptopathy is a primary neural consequence of noise exposure and aging, defined by loss of IHC–ANF ribbon synapses and reduced suprathreshold neural output despite preserved thresholds. This dissociation reflects the selective vulnerability of low-SR, high-threshold ANFs, which compromises temporal precision, neural synchrony, and listening-in-noise ability. Evidence from human studies suggests that cochlear synaptopathy as a probable or possible contributor to auditory complaints contributes to auditory complaints in high-risk groups, although findings vary with differences in exposure characterization, cohort selection, and electrophysiologic paradigms. Clinically, this neural deficit provides a biologically plausible explanation for speech-in-noise difficulties, tinnitus, and hyperacusis in listeners with normal audiograms. Translational uncertainty persists due to the absence of in vivo histopathology, individual variability, and central compensation that may obscure peripheral injury. Thus, cochlear synaptopathy in humans is best conceptualized as a spectrum of neural dysfunction rather than a binary diagnosis, inferred most reliably when multiple physiologic measures converge with well-documented exposure history. Importantly, emerging therapeutic studies in animal models show that synaptic connections can be regenerated: local NT-3 delivery or supporting-cell Ntf3 overexpression restores ribbon synapses and improves ABR wave-I amplitudes after noise trauma. Accordingly, a multimodal clinical battery incorporating fast-rate ECochG and ABR stimulation in noise, EFRs, and MEMR growth functions offers the most defensible strategy for identification and classification of synaptopathic dysfunction and for tracking potential therapeutic efficacy.

## Limitations

This review is limited by the current literature and its narrative methodology. Human synaptopathy cannot be confirmed histologically, requiring reliance on indirect physiological markers with evolving sensitivity and specificity. Differences in exposure paradigms, species translation, participant characteristics, and recording protocols limit comparability across studies. Noise exposure histories are often imprecise and may obscure dose response relationships. Central compensation, particularly in younger listeners, may further reduce sensitivity of measures such as ABR wave I amplitude. Because this was a PRISMA informed narrative review, formal risk of bias scoring and meta-analysis were not performed, although transparent search and critical synthesis were applied.

## Future Research

Future work on cochlear synaptopathy should standardize exposure quantification using objective logging and adopt longitudinal designs across the lifespan. Multimodal electrophysiology combining ABR, ECochG, EFR, and MEMR measures should be harmonized across laboratories, including near-field recordings and linkage to speech-in-noise performance. Cross species paradigms and prospective clinical classification of probable versus possible synaptopathy require validation. Prevention studies should examine the interaction between noise exposure and aging, and translational progress will depend on correlating physiological findings with postmortem temporal bone pathology. Sensitive neural endpoints are also needed for synapse restorative therapies targeting synaptic repair.

## Acknowledgment

All schematic figures were manually illustrated by the author using Microsoft PowerPoint and Adobe Photoshop, with all scientific content and interpretations generated by the author.

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