Cochlear synaptopathy: new findings in animal and human research

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Abstract: In animal models, prolonged exposure (2 h) to high-level noise causes an irreparable damage to the synapses between the inner hair cells and auditory nerve fibers within the cochlea. Nevertheless, this injury does not necessarily alter the hearing threshold. Similar findings have been observed as part of typical aging in animals. This type of cochlear synaptopathy, popularly called "hidden hearing loss," has been a significant issue in neuroscience research and clinical audiology scientists. The results obtained in different investigations are inconclusive in their diagnosis and suggest new strategies for both prognosis and treatment of cochlear synaptopathy. Here we review the major physiological findings regarding cochlear synaptopathy in animals and humans and discuss mathematical models. We also analyze the potential impact of these results on clinical practice and therapeutic options.

Keywords: audiology; auditory assessment; cochlear synaptopathy; deafferentation; noise-induced hearing loss.

Introduction

The exposure to intense noise and/or aging has been thought to produce degenerative changes in auditory hair cells, mainly the outer hair cells (OHC) and the nerve cells originated from an aggregation of nerve cell bodies called spiral ganglion cells or SGC (Liberman (2016)). In the case of sensorial hearing loss, the classic view is that there is a ''primary degeneration'' when the injury is at the level of the OHC and a ''secondary degeneration'' when there is a loss of cochlear nerve fibers (Kujawa and Liberman 2015). However, in a seminal study in mice realized by Kujawa and Liberman (2009), it was shown that a 2 h exposure to high intensity noise causes irreversible damage to cochlear synapses with a transient threshold shifts (TTS) that completely normalize at 14 days post-exposure (Kujawa and Liberman 2009). This study showed that exposure to high intensity noise in a short period of time, generates injuries to our auditory system which would not be evidenced in clinical audiological tests and could generate speech-in-noise difficulties, tinnitus or hyperacusis. For this reason, this cochlear synaptopathy (CS) has been called hidden hearing loss (Schaette and McAlpine 2011). Here, we review the principal physiological findings regarding CS in animals and humans and analyze mathematical models, discussing the potential impact of these results on clinical practice and therapeutic options.

Animal models of hidden hearing loss

Table 1 summarizes the principal studies with animal models to CS**.** The study performed in mice by Kujawa and Liberman (2009) showed that exposure to intense (100 dB) octave band of noise (8–16 kHz) for 2 h period caused irreversible degeneration in up to 50% the synaptic connections between the inner hair cells (IHC) and the auditory nerve fibers (ribbon synapses). We can define to CS as damage around the synapses between inner hair cells (IHCs) and type-I afferent auditory nerve fibers. This CS was accompanied by a transitory increase in auditory threshold evidenced by auditory brainstem responses (ABR) wave I amplitude reduction, and compound action potentials (CAPs) of auditory nerve, but interestingly, this overt hearing loss completely normalized within two weeks post-exposure (Kujawa and Liberman 2009). A guinea pig model produced results of similar magnitude after 2 h of exposure to intense noise (106 dB SPL), with the additional finding that the damage was selective for fibers with low-spontaneous discharge rates

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(Furman et al. 2013). A study with primates (*Macaca mulatta*) showed that continuous exposure to ≥140 dB noise for 4 h was required to generate CS (Valero et al. 2017). In Chinchillas, Hickman et al. (2018) using blasts from 160–175 dB SPL, found that exposures that cause large >40 dB temporary TTS, generating 20–45% auditory synapses loss (Hickman et al. 2018). Bakay et al. (2018) showed in mice that the noise-induced cochlear synaptopathy (NICS) also promotes a less capacity for adaptation to loud environments in the midbrain neurons (inferior colliculus). This mis-adaptation generates a cascade of other events that cause an increase of central gain, generating tinnitus and/or hyperacusis. These difficulties would allow us to understand why subjects with normal hearing have trouble understanding conversations in noisy environments (Bakay et al. 2018). All these findings suggest that the synapses between the inner hair cells and auditory nerve fibers are among the most vulnerable structures in the cochlea and that damage to these synapses may underlie both acoustic trauma and age-related hearing loss (Kujawa and Liberman 2015). However, the "hidden hearing loss" would not be caused exclusively by damage to auditory synapses. Wan and Corfas (2017) have demonstrated that some permanent auditory deficits that are currently attributed to CS may instead be associated with a transient loss of cochlear Schwann cells. In this study, using transgenic mice the authors report that a transient demyelination generates a permanent auditory deficit as in other clinical pathologies caused by demyelinating events such as demyelinating polyneuropathy, chronic inflammatory demyelinating polyneuropathy or Guillain-Barre syndrome (Kabzińska et al. 2007; Nelson et al. 1988). These diseases have been shown to generate auditory deficits, such as reduced ABR amplitudes, increased latencies and speech-in-noise difficulties, similar characteristics of CS but not associated with synaptic loss (Wan and Corfas 2017).

Cochlear synaptopathy in humans

Physiological findings and mathematical models of cochlear synaptopathy

Findings from animal models lead to the following important question: how "hidden" is this condition really? Despite normal sensitivity on audiometric testing, problems are often quite apparent in the context of complex auditory-perceptual tasks. Mathematical models are useful for exploring this question.

The young healthy human auditory nerve contains around 30,000 afferent fibers each of which responds stochastically to the auditory stimulus (Makary et al. 2011). Lopez-Poveda and Barrios (2013) have developed a "stochastic undersampling" model in which the audio signal is randomly, or stochastically, undersampled, resulting in a low-quality neural representation of the original stimulus that mimics the conditions of auditory deafferentation. This model has two important assumptions i) the auditory perception is directly related tom the quality of the neural representation of the sound waveform and ii) the quality of the waveform representation in the auditory nerve depends on the number of aggregated spike trains. The model predicts that simple functions such as tone detection would remain intact under these conditions, but complex functions, such as perception of speech in noise, would be significantly impaired. The model was tested by evaluating the tonal threshold and speech in noise perception of in 20 young normal-hearing voluntaries. Both acoustics stimuli were filtered through a bank of 10 filters working in parallel and each band was randomly subsampled at high and low sampling rate in order to mimic a high and low deafferentation respectively. The experimental results support the model predictions (Lopez-Poveda and Barrios 2013). Oxenham uses a simple model based on the signal detection theory to evaluate the potential effects of CS on various auditory-perceptual abilities in humans. The model suggests that tone detection, and therefore performance on conventional tonal audiometry, may remain intact even after a 50% loss of synapses (Oxenham 2016). Verhulst et al. (2016) using a functional model, described that some ABR parameters (ABR growth ratio, Wave-I amplitude or Wave-V/I ratio and the ABR growth ratio, calculated from ABR Wave-V latency *vs.* intensity and amplitude *vs.* intensity curves) would be more sensitive to CS or OHC-related deficits. Whereas the ABR latency growth metric strongly depends on the high-frequency cochlear gain loss (OHC-related deficits) ABR Wave I amplitude along with the Wave-V/I ratio would allow isolating the CS (Verhulst et al. 2016).

Electrophysiological assessment of cochlear synaptopathy in humans

Electrophysiological assessment has been proposed as a complimentary method to assess for hidden hearing loss (HHL) in human patients, given the apparent inadequacy of simple tone detection. Two of the main techniques used today for the study of CS correspond to ABR and frequency following response (FFR). The ABR is defined as a set of electrical responses generated at various anatomical sites through an external auditory stimulus. This acoustic stimulation generates responses through sequential and synchronized activation of the nerve fibers along the auditory pathway (Jewett and Williston 1971). The FFR

Table 1: Summary of main results observed in the study of cochlearsynaptopathy in animals.

Authors	Model	Principals techniques	Noise overexposure	Principal results
Kujawa and Liberman. 2009	Male CBA/CaJ mice.	Electrophysiological test (ABR, DPOAEs, CAP).Confocal microscopy.	100 dB SPL (octave band noise 8–16 kHz) in 2 h.	A reduction in ABR wave I amplitude without DPOAEs amplitude reduction is generated in animals exposed to noise. Hearing thresholds fully recovered 2 weeks post noise-exposure.
Furman et al., 2013	Female, albino guinea pigs (Hartley strain).	Electrophysiological test (ABR, DPOAEs and single-fiber recordings) .Confocal microscopy.	106 dB SPL (octave band noise 4–8 kHz) in 2 h.	Auditory nerve fiber single-unit responses revealed a reduction in the proportion of low and medium-SR fibers activity in comparison to high-SR fibers in animal exposed to high noise.
Sergeyenko et al., 2013	Male mice (CBA/CaJ) with various ages (4–144 weeks).	Electrophysiological test (ABR and DPOAEs). Confocal microscopy.	No.	A loss of IHC synaptic ribbons, a reduction in ABR wave I amplitude and reduction in DPOAEs amplitude was generated in aging mice (beyond 80 weeks) in absence of high level noise exposure.
Shaheen et al., 2015	Male mice (CBA/CaJ) control and with various ages (8–16 weeks).	Electrophysiological test (ABR, FFR and DPOAEs). Confocal microscopy.	Group 1a-exposed to 98 dB SPL at 8 weeks of age; group 1b-also exposed to 98 dB SPL at 8 weeks; and group 2-exposed to 99 dB SPL at 16 weeks.	Noise-exposure reduces EFR amplitudes and phase-locking values. EFR is sensitive to synaptopathy at high modulation rates (around 1 kHz).
Wan and Corfas 2017	Transgenic (Plp1/CreER^{T}, Ai14:Rosa26^{tdTomato} Rosa26$^{DTA)}$ and control mice.	Electrophysiological test (ABR and DPOAEs). Confocal microscopy.	100 dB SPL (octave band noise 8–16 kHz) in 2 h.	Using transgenic mice, a transient Schwann cell ablation, was induced, generating an auditory neuropathy and permanent hidden hearing loss. The induced hidden hearing loss by demyelination was not generated by synaptic ribbon losses.
Valero et al., 2017	Monkeys (*Macaca mulatta*).	Electrophysiological test (ABR and DPOAEs). Confocal microscopy.	50-kHz noise band centered at 2 kHz during 4 h. Noise levels varied for different exposures.	Animals developed ABR I supratrheshold amplitude reduction and temporary threshold shifts only at high intensity levels (beyond 140 dB SPL).
Bakay et al., 2018	Male CBA/Ca mice.	Electrophysiological test (ABR and extracellular recordings in inferior colliculus).	100 dB SPL (octave band noise 8-16 kHz) in 2 h.	Animals with HHL showed a low neuronal adaptation levels in the inferior colliculus in noisy environments.
Hickman et al., 2018	Chinchilla	Electrophysiological test (CAP and DPOAEs). Confocal microscopy	10 Blast to 160–175 dB SPL of broad-spectrum (0.3–100 kHz)	Blast noise exposure caused temporary threshold shifts without permanent hair cells and synaptopathic damage (20–45% ribbon synapse loss)

reflects sustained phase-locked activity in a population of neural units within the brainstem and is characterized by a periodic waveform that follows the individual cycles of the stimulus waveform (Marsh et al. 1970). Table 2 summarizes the principal studies in CS realized in humans, with electrophysiological and behavioral assessments.

ABR wave I and FFR assessment

One of the electrophysiological measures most commonly used as a marker for CS is the ABR wave I amplitude, since it is a very good tool in the evaluation of the integrity of the auditory nerve. However, there are limitations in the utility

of this measure. First, this response has low amplitude in humans compared to animal records, since it is a far-field auditory record obtained mainly in a transtympanic way and tested without anesthesia whereas animals are tested with anesthesia and the electric potential is registered directly with an electrode placed in the cochlea or using subcutaneous needle electrodes (Bramhall et al. 2019). Second, there is significant variability among subjects, potentially attributable to factors such as electrical artifact, gender, synchronization of auditory nerve fibers, head size and type of eliciting stimulus. ABR wave I amplitude has excellent test-retest reliability in humans (low measurement error) but large between-subject variance (Prendergast et al. 2018).

Another electrophysiological technique used in CS research is the FFR. Unlike ABR, this technique is a phase-locked neural activity generated in response to amplitude modulated sounds that can be measured from electrodes placed on the scalp. In most studies to date, the stimulus has a fundamental frequency (f_0) between 80 and 500 Hz. Stimulus duration is usually between 40 and 250 ms, generally suprathreshold (70–80 dB SPL) and presented mono or binaurally with alternating polarity modulation. In humans, low modulations rates (70–200 Hz) range elicit phase-locked responses in a cascade of subcortical auditory structures, from cochlear hair cells to inferior colliculus (IC) neurons (Coffey et al. 2019). The FFR have a short stimulus-to-response latency of ~5–9 ms, so it has been proposed that it has a subcortical origin (King et al. 2016).

Summary of studies consistent with cochlear synaptopathy using ABR technique

One of the main hypotheses in the study of the CS in humans is that the ABR wave I amplitude should be diminished according the study of Kujawa and Liberman (2009). Schaette and McAlpine (2011) found that the amplitudes of ABR wave I were significantly smaller for high sound intensities (90 and 100 dB SPL) in subjects with tinnitus *vs*. control group. The ABR wave V amplitude did not change significantly in comparison to control group, suggesting that homeostatic mechanisms in central auditory structures adjust neural responsiveness (central gain) to compensate for reduced input from the auditory neural fibers. For this authors the increment of the central gain, manifested as reduced neural output from the cochlea and consequent renormalization of neuronal response magnitude within the brainstem, suggest that it would be a direct physiological evidence of hidden hearing loss (Schaette and McAlpine 2011). Stamper and Johnson (2015a) were one of the first authors to show a correlation between degree of noise exposure and ABR wave I amplitude in humans; however, the recording techniques that were used are susceptible to significant variability and also, there was gender confound in their initial 2015 publication (Stamper and Johnson 2015a). In a second study, the authors performed separate analyzes for males and females. The reanalysis from this work found a significant decrease in ABR wave I amplitude as a function of noise exposure only in females, but not in males (Stamper and Johnson 2015b). Liberman et al. (2016) suggested that an increased ratio between the summating potential (SP) and compound action potential (CAP) of the auditory nerve, as measured through electrocochleography (a test easily accessible to the clinical audiologist), may indicate ''high risk'' for noise-induced synaptopathy. SP/CAP ratio is produced by an increase in the SP rather than a decrease in the CAP. It is not clear how this finding is associated with CS, as one might expect to find reduced estimates of CAP in the high noise group (Liberman et al. 2016)

Bramhall et al. (2017) described a decrease in the supra threshold amplitude of the ABR I wave amplitude (110 dB peSPL) obtained with a 4 kHz tone in civilians and military people with high noise exposure. Valderrama et al. (2018) report similar results in subjects with noise exposure (with and without tinnitus). In this study, a moderate negative correlation was found between the amplitude of wave I and the magnitude of lifetime noise exposure. Moreover, the tinnitus group presented a statistically significant lower I/V ratios values than the non-tinnitus group (Valderrama et al. 2018).

ABR wave V latency has also been evaluated as a potential marker of CS. Mehrai et al. (2016) found that the changes in the V wave amplitude in response to increases of masking noise levels, are very similar to the decrease in ABR wave I latency. These authors interpret the results as an alteration in the functionality of auditory fibers with low-spontaneous rate, since these fibers are resistant to noise masking and a dysfunction of these would imply a reduction of the levels of latency with the increase of levels of masking. However, this study did not evaluate noise exposure over time in the subjects tested (Mehraei et al. 2016).

Summary of studies NOT consistent with cochlear synaptopathy using ABR technique

Several studies have found no association between the amplitude of wave I and the degree of exposure to noise. Fulbright et al. (2017) suggests that ABR wave I amplitude

Table 2: Summary of main results observed in the study of cochlearsynaptopathy in humans.

Authors	*n*	age	Subjects history	Electrophysiological test	Behavioral test	Principal findings
Schaette and McAlpine 2011	33	36.3 ± 2.6 tinnitus group, 33.2 ± 1.9 non tinnitus group.	Subjects otologically healthy with and without tinnitus.	ABR: 50 μs-clicks at 90–100 dB sound pressure level (SPL) at 11 presentation rates per second.		The wave I of the ABR was significantly smaller for high sound intensities in subjects with tinnitus *vs.* control group. The wave V did not change significantly in comparison to control group. This increase of 'central gain' could explain tinnitus or hypercusis originated by sensorial deprivation.
Stamper and Johnson 2015 (a,b)	30	19–28	Study of subjects exposed to noise in 12 months ranged from 67 to 83 LAeq8760.	Electrophysiological test: ABR 100 μs-clicks, 4 kHz and 90 dB nHL.		This authors report a correlation between the amplitude of the I wave and the degree of exposure to noise using a questionnaire (NBS), but effect of exposure was demonstrated only for females (not for males).
Liberman et al., 2016.	34	18–41	High risk music students *vs*. low risk non-music students.	ABR 100 μs-clicks delivered at 94.5 dB nHL.	Northwestern University Auditory Test Number 6 (NU-6) list (Word recognition performance). The test was realized in quiet, noise (ipsilateral white noise) or compression + reverberation (time compression of 45% or 65% and a reverberation time of 0.3 s) conditions.	There is a decrease in the SP / AP ratio of the ECOG in subjects with a high probability of damage from exposure to noise. The hearing threshold and DPOAEs was normal in high and low risk groups.
Prendergast et al., 2017a	126	18–36	Subjects with noise exposure ranged from 0 to 2.5 log10(Energy).	Electrophysiological test: ABR 100 μs-clicks, 80 dB nHL FFR: low-frequency tone and a transposed tone presented to 80 dB SPL in each ear.		These authors do not find auditory alterations caused by cochlear synaptophaty by noise exposure in ABR or FFR measures.
Prendergast et al., 2017b	138	18–36	Subjects with noise exposure ranged from 0 to 2.5 log10(Energy).		(Frequency difference limens, Intensity difference limens, Interaural phase difference discrimination, Amplitude modulation detection, Digit triplet test, Co-ordinate response measure, Musical consonance task).	Using many behavioral tasks, these authors do not find auditory behavior alterations caused by noise exposure.

Table 2: (continued)

Authors	*n* age	Subjects history	Electrophysiological test	Behavioral test	Principal findings
Grinn et al., 2017	32 21–27	Study of subjects exposed to noise in 12 months ranged from 64 to 88 LAeq8760	ABR: Clicks and burst tones of 2, 3 and 4 kHz at 70, 80 and 90 dB nHL.	Northwestern University Auditory Test Number 6 (NU- 6) words (for Word recognition performance); WIN TEST with 80 dB SPL in bubble noise.	Using speech perception in noise (SPiN) test, these authors do not find auditory perceptual alterations and impaired SPiN was not associated with ABR or EFR measures of cochlear synaptopathy.
Valderrama et al. 2018	74 29–55	Subjects with noise exposure ranged from 3 to 4.5 log10(Energy)	ABR: 12,500 rarefaction clicks of 113 ms, 39.1 stim/s at 108.5 dB SPL, corresponding to 75 dB HL.		This study reports a significant negative correlation between self-reported levels of lifetime noise exposure and the amplitude of wave I ABR.
Brahamall et al., 2017	64 19–35	Military veterans with high- *vs*. low-noise exposure history.	ABR: 1 kHz tone burst (70, 80, 90, 100, and 110 dB peSPL), 4 kHz tone burst (60, 70, 80, 90, 100, and 110 dB peSPL), 3 and 6 kHz tone burst to 110 dB peSPL).		This study reported that there is a decrease in the amplitude of the ABR wave I at suprathreshold levels of intensity (110 dB SPL) in military personnel exposed to noise at the frequency of 4 kHz.
Guest et al., 2017	40 18–35	Subjects with noise exposure ranged from 0.2 to 123 NESI units.	Filtered clicks (1.2 to 4.7 kHz), presentation rate of 14.1/s and 7040 presentations per ear (102 db peSPL) EFR transposed tones (400 ms, F_c 4 kHz, F_m 100 Hz).		Noise exposure in subjects with tinnitus was not associated with ABR I amplitude, wave I/V ratio or EFR amplitude.
Guest et al., 2018	64 18–40	Subjects with noise exposure ranged from 0 to 90 NESI units.	Filtered clicks (1.2 to 4.7 kHz), presentation rate of 14.1/s and 7040 presentations per ear (102 dB peSPL) EFR transposed tones (400 ms, F_c 4 kHz, F_m 100 Hz).	SPIN TEST with Speech stimuli and speech maskers at 80 dB SPL.	Impaired SPiN was not associated with ABR I amplitude, wave I/V ratio or EFR amplitude.
Skoe and Tufts 2018	73 18–24	Subjects low and high-exposure groups using the noise dosimetry data.	ABR: 100 µs clicks at 75 dB nHL (106.7 dB peSPL) at 8 presentation rates/s.		Noise exposure in subjects was not associated with ABR I wave amplitude or latency.

and noise exposure history were not reliably correlated with suprathreshold functional hearing tests (ABR: 4 kHz to 90 dB nHL, rate of 21.1/s) (Fulbright et al. 2017). Prendergast et al. (2017) suggest that ABR wave I amplitude is unrelated to the magnitude of noise exposure (Prendergast et al. 2017a). Guest et al. (2017) observed similar

results in subjects exposed to noise, with tinnitus and normal hearing. Grinn et al. (2017) did not find significant differences in CAP amplitude obtained by electrocochleography in subjects exposed to recreational noise. Skoe and Tufts (2018) suggest that noise exposure is associated with ABR latency but not wave I amplitude. Prendergast et al. (2018) suggest that the noise exposure is not related to ABR wave I amplitude or SP/CAP ratio.

Summary of studies in cochlear synaptopathy using FFR technique

The FFR has been suggested as an alternative to the ABR in order to evaluate the temporal coding of auditory periphery. The objective of FFR recordings is to investigate the ability of the auditory system to phase lock to low-frequency pure tones and to the modulated envelope of a high-frequency pure tone carrier. Loss of fibers with low-spontaneous discharge rates may affect perception of the fine temporal structure and stimulus envelope at suprathreshold intensities, which would be detrimental to coding of the stimulus envelope at medium and high intensities (Bharadwaj et al. 2014). The FFR may not directly reflect auditory nerve fiber activity, although abnormal findings could reflect degradation of central temporal coding due to neuropathic or synaptopathic auditory damage (Plack et al. 2014).In most studies, the FFR has not been reliably shown to detect CS, and the utility of the ABR is limited due to inter-subject variability, leaving us without a conclusive electrophysiological test to evaluate HHL. One explanation for this result is that in animal studies the FFR was most sensitive to CS for stimulus modulation frequencies between 700 and 1000 Hz while in humans, the FFR is obtained at much lower modulation frequencies (80–120 Hz). Another explanation is that top-down activity, including cognition and memory capabilities, can influence neural responses in the FFR responses (Bramhall et al. 2019)

Bharadwaj et al. (2015) described an FFR approach in which he uses different depths of modulation presented in a notched masking noise (FFR: 4 kHz AM tones in notched noise, modulated at 100 Hz at 75 dB SPL). The results suggest that the slope of the function which describes how the FFR changes as a function of modulation depth could be sensitive to underlying CS. However, this work does not strongly document the degree of noise exposure history of the subjects studied (participants were grouped as "more" and "less" recreational-noise exposed) (Bharadwaj et al. 2015). Other studies show that there is no relationship between the amplitude of the FFR and NICS. Prendergast et al. (2017a) found that the amplitude of the FFR envelope decreased as noise exposure increased, the correlation was weak and was appreciable only in male subjects (low-frequency tone and a transposed tone presented to 80 dB SPL in each ear) (Prendergast et al. 2017a). Similar results have been observed in subjects with tinnitus and normal hearing (EFR transposed tones (400 ms, Fc 4 kHz, Fm 100 Hz) (Guest et al. 2017).

Behavioral assessment of hidden hearing loss in humans

Several studies have indicated that exposure to intense noise may affect functional auditory performance on behavioral tasks but no correlation has been observed between alterations of these tests and CS. The results have been inconsistent with each other. (Kumar et al. 2012) observed that a group of 30–60 year-old subjects with a history of significant noise exposure showed deficits in temporal coding of sound, likely associated with damage to neurons that code for both the temporal envelope and fine structure of sounds (Kumar et al. 2012). In contrast, four studies were unable to identify a relationship between auditory perceptual difficulties and noise exposure history. Grinn et al. (2017) conducted a series of evaluations in subjects who self-reported exposure to intense noise (Noise Exposure Questionnaire) and found no word discrimination in noise (WIN-Test) deficits on the day following the exposure. Moreover, these authors found no electrophysiological abnormalities after evaluating otoacoustic emissions and CAP amplitude with electrocochleography. Similarly, Prendergast et al. (2017b) exhaustively examined performance on various perceptual task, such as intensity and frequency change detection, detection of amplitude modulation and digit triplet tests and found no significant differences between the noise-exposed and healthy subjects (Prendergast et al. 2017b. Grose et al. 2017) did not find differences in performances on speech in noise test (Bamford-Kowel-Bench test) or any psychoacoustic task (temporal modulation detection, spectral modulation detection, and interaural phase sensitivity) between subjects exposed to recreational noise (high intensity music concert) *vs.* a control group (Grose et al. 2017). Yeend et al. (2017) examined performances in speech-in-noise perception. Listening in Spatialized Noise-Sentences (LiSN-S) and National Acoustic Laboratories Dynamic Conversations Test (NAL-DCT test), nor in conducted tests of attention (Test of Everyday Attention and memory (Reading Span Test) in people with and without a history of noise exposure

(lifetime noise exposure ranged from 1.9 to 4.9 log10Pa^{2}h). The results showed no relation between participant lifetime noise exposure and performance in speech-in-noise or psychoacoustic tasks.

Future of basic, clinical and rehabilitation studies in cochlear synaptopathy

In recent years, there has been great interest in establishing clinical correlates of the noise-related cochlear nerve degeneration reported by Kujawa and Liberman in animal models. However, there is currently no effective method for detecting NICS in humans. Three possible explanations have been proposed for this apparent discrepancy: i) NICS may not be prevalent in young people; ii) NICS may be prevalent only for low-intensity stimuli, and tests using higher-intensity stimuli would not reveal major abnormalities; or iii) the available diagnostic tools are insensitive to NICS. In the point i, the results of Valderrama et al. (2018) would go along this line. In this study, a correlation between lifetime noise exposure and electrophysiological measures was showed on middle-age, but not in young people. However, several other studies found no such correlation (Fulbright et al. 2017; Grinn et al. 2017; Guest et al. 2017; Prendergast et al. 2017, 2018; Skoe and Tufts, 2018). The point ii is supported by the results obtained in Valero et al. (2017). This study showed that continuous exposure to ≥140 dB noise for 4 h was required to generate auditory synaptopathy. This finding suggests that prevalence in humans is less than initially suspected due to higher tolerance than rodents to noise exposure (Valero et al. 2017). The point iii is currently an active research topic in auditory neurosciences and clinical audiology. Electrophysiological and behavioral techniques have not had conclusive results in the CS study. Most of the studies on this topic in the literature have been unable to demonstrate a causal relationship between noise exposure levels and synaptopathic damage.

The relevance of the Kujawa and Liberman (2009) study to humans remains under discussion. On the other hand, age-related CS may be more easily detected. Animal studies suggest that CS may occur naturally in long-lived mice not exposed to noise (Sergeyenko et al. 2013); that is, aging alone may cause a loss of functionality at the synapses between the IHC and auditory nerve fibers. Makary et al. (2011), founded that spiral ganglion cells are lost at a rate of approximately 32.913 – (100.25 ∗ age in years), reflective of the continuous deafferentation that a healthy subject undergoes with the passage of time (Makary et al. 2011). The evidence suggests that many clinical complaints of impaired language comprehension in noisy environments may be due to age-related auditory deafferentation rather than noise exposure as it is likely that a greater noise intensity and a longer period of exposure than is typical would be necessary to cause this type of damage in humans. It should also be emphasized that exposure to high- or even medium-intensity noise may alter the tonotopic maps of the auditory cortex, which could explain problems with discrimination in noisy environments (Eggermont 2008; Gourévitch et al. 2014).

Suggestions for methodological assessments to investigate the cochlear synaptopathy in humans

CS represents a condition of subclinical hearing damage, which deserves to be studied in depth, since having adequate diagnostic tools will allow an early intervention, which can delay or prevent a hearing impairment. As we have seen, both electrophysiological and perceptual tests in humans have not been conclusive in CS detection, which makes clinical diagnosis difficult. As we discussed in the previous section, one possibility is to develop an NICS, in which the clinical patients should be exposed to sound intensities greater than those analyzed in current studies (Valero et al. 2017). Another option is that the current diagnostic tools are not accurate enough for the diagnosis of CS, so we must modify our current protocols for better prognosis. A recent review by Bramhall et al. (2019) suggests a series of methodological approaches for the study of this condition, for example, the study of high frequencies (12–16 kHz) in clinical audiometry, since these thresholds would be related to the exposure history of subject noise (Bramhall et al. 2019). In the ABR test, the recommendations would be to use click tones and consider additional options such as pure or chirp tones for later comparisons. The intensity of the ABR tones should be between 90 and 100 dB peSPL, since they would be more sensitive in revealing deficits in the wave I, their duration should be around 80–100 μS and the number of averaged epochs, should at least use 4000 samples averaged, in order to reduce the noise of the register and allow the easiest identification of wave I (Bramhall et al. 2019). By the other hand, to differentiate between OHC and auditory nerve fibers damage, the most recommended method is the use of distortion-product

otoacoustic emissions or DPOAEs with intensities of 65 and 55 dB SPL in their f1 and f2 tones respectively, since with these intensities we can compare our results with other normative studies (Gorga et al. 1997). Finally, there are a variety of electrophysiological tests under investigation for potential use detecting HHL that we can use in the future as complementary batteries, for example middle ear muscle reflex (MEMR) (Valero et al. 2016, 2017), audiometric test with brief tones (Lopez-Poveda and Barrios 2013), or envelope following response (EFR) (Bharadwaj et al. 2015; Paul et al. 2017). However, there is not enough evidence for their implementation. For example, the MEMR is diminished or absent in a subgroup of the population with normal hearing, which would make its interpretation difficult in patients with auditory synaptopathy (Flamme et al. 2017). In the case of audiometric test with brief tones, we can mention a study performed by Wong *et al.*, in which he infused kainic acid in the left and right ear in five animals (*budgerigars*). In this study, although the ABR wave I decreased a 40–70% without impacting DPOAEs, behavioral tone detection was unaffected as a function of frequency and duration (Wong et al. 2019). Finally, we had mentioned the EFR. We can define the EFR as a steady-state evoked response which follows the envelope of a stimulating waveform. The measurement of high modulation rates associated with synaptopathy in animal models (around 1000 Hz) is very difficult in humans (in humans, the typical rate used in EFR measurements are 100 Hz). The interpretation of the EFR used in humans will depend critically on both the modulation rate used and masking noise applied (Bramhall et al. 2019).

Rehabilitation in subjects with cochlear synaptopathy

A challenge in the future will be the treatment and rehabilitation of subjects with auditory synaptopathy. The basic studies have tried to restore auditory function in animal models of noise-induced CS by local injection of trophic factors or genetic engineering (for review, see Kujawa and Liberman 2019. Suzuki et al. 2016), by injection of neurotrophin-3 (NT-3) in the round window niche, 24 h after an exposure that causes an immediate loss of up to 50% loss of ribbon synapses in basal cochlear regions. The NT-3 reverted the synaptic losses and restored the functional recovery of suprathreshold responses in I wave ABR and DPOAEs amplitudes (Suzuki et al. 2016). Hashimoto *et al.*, injected unilaterally adeno-associated virus (AAV) containing either NT3 or green fluorescent protein (GFP) genes, via the posterior semicircular canal in mice with noise-induced HHL. In unexposed ears, NT3 overexpression did not affect thresholds, however GFP overexpression caused IHC loss. In exposed ears, NT3 overexpression increased permanent threshold shifts. These studies are very interesting, because in the future they could be applied to human beings with HHL, for example through an intrathympanic injection (Hashimoto et al. 2019). By the other hand, in the clinical treatment, the hearing aids are adapted mainly by the degree of hearing loss but not by the difficulties of speech-in-noise. One option for this problem is the use of hearing aids with low amplification, which would be beneficial in these subjects (Reed et al. 2017). Another option for rehabilitation would be the use of auditory training programs in the clinical patients, developed by universities or private companies for example, clEAR (https://www.clearworks4ears.com/) or Sense Synergy ReadMyQuips (http://www.sensesynergy.com/readmyquips), however, more evidence-based decisions are needed to help patients with normal hearing thresholds and speech-in-noise difficulties.

Conclusions

In the future, it will be interesting to determine whether other electrophysiological or behavioral tests might be capable of accounting for age-related auditory changes (in the context of a normal audiometric threshold) and whether various protective factors or events may mitigate synaptopathic damage. On the other hand, we believe that for future studies of CS in humans, it is convenient to adopt the suggestions mentioned in the work by Bramhall et al. (2019) on the implementation of electrophysiological protocols and audiological test batteries. In this way, we can implement the most sensitive non-invasive measures for detecting CS in humans.

Finally, we must emphasize the limitations of audiometric testing as an audiological evaluation system. While pure tone audiometry is currently the gold standard for evaluating auditory sensitivity, hearing thresholds may remain within normal limits even with a loss of up to 50% of inner hair cells (Lobarinas et al. 2013; Oxenham 2016). Therefore, it is crucial to complement conventional audiological tests with new methodological approaches for the CS (discussed in this review) and the use of new audiological batteries in the future if their clinical evidence is favorable.

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