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Biomarkers for hidden hearing loss: towards early and effective diagnosis

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- There is a segment of the population that experiences communication difficulties in noisy environments, such as a café or a restaurant, who, when seeking help at a clinic, are diagnosed with “normal hearing” because their hearing thresholds are below 20 dB HL.
- These hearing difficulties are known as “hidden hearing loss,” because there is a hearing impairment that remains hidden beneath a normal audiogram.
- In this talk, I will present the fundamental concepts underlying hidden hearing loss, together with a set of hypotheses on how the sensitivity of the compound action potential amplitude might be enhanced to better capture cochlear synaptopathy.

Impact on quality of life

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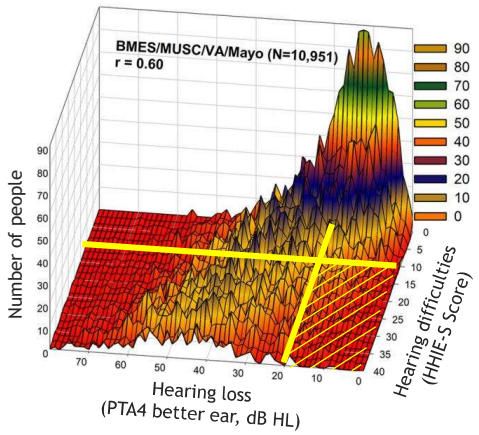
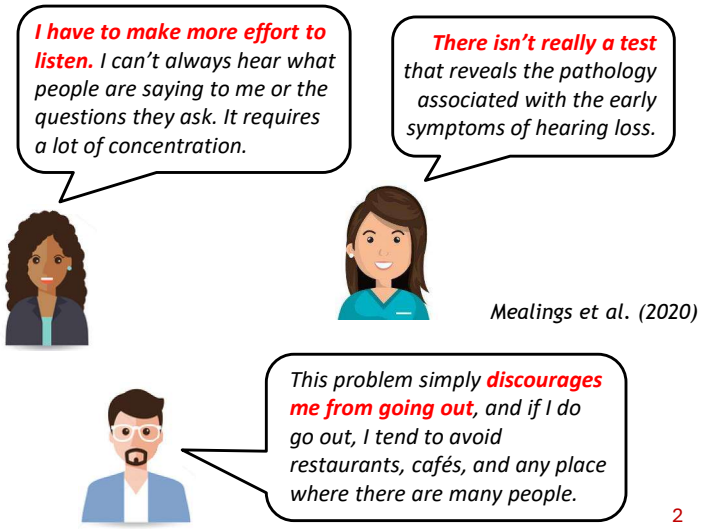


Humes (2021)



Mealings et al. (2020)

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- The figure from Humes (2021) perfectly illustrates this segment of the population. It shows the number of individuals in a sample of 11,000 people in terms of (1) self-reported hearing difficulties according to a brief questionnaire, and (2) their audiometric thresholds. Naturally, the greater the hearing loss, the greater the perceived hearing difficulties. The sector of the population we are referring to is the one that reports experiencing hearing problems (HHIE-S > 10) but has a "normal" audiogram (no measurable hearing loss).

- In the study by Mealings et al. (2020), we interviewed both people who experience these hearing difficulties and the clinical staff who attend to them, to gain first-hand insight into the impact these difficulties have on their lives and on clinical practice.

- We learned that the impact of hidden hearing loss is far from negligible, significantly affecting several dimensions of auditory well-being, such as listening effort and social participation. For example, two participants reported: "I have to make more effort to listen..." and "This problem simply discourages me...".

- Clinical staff, on the other hand, reported feeling frustrated at not having sensitive diagnostic tools that would allow them to provide an appropriate intervention. For example, they told us: “There isn’t really a test…”.

- These testimonies highlight the need for accurate diagnosis of the underlying causes of these hearing difficulties.

Cochlear synaptopathy (CS)

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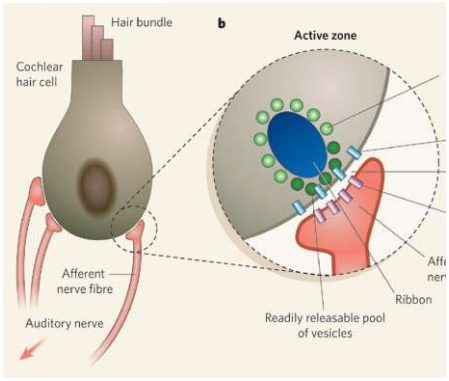
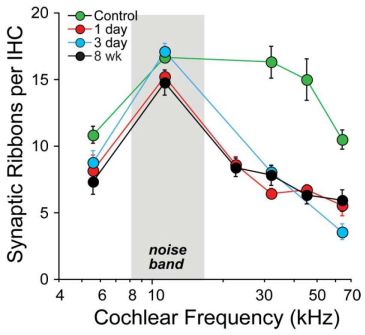
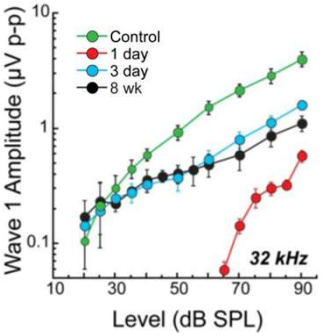
- CBA mice
- Noise 8–16 kHz
- 100 dB SPL, 2 hours



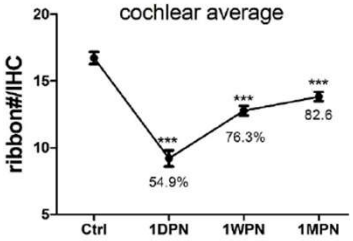
Kujawa and Liberman (2009)





- Guinea Pigs

Song et al. (2016)



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- The pathology most strongly associated with hidden hearing loss is cochlear synaptopathy. Cochlear synaptopathy was first described by Kujawa and Liberman in 2009.
- In their study, the authors exposed CBA mice to octave-band noise spanning 8–16 kHz at 100 dB SPL for 2 hours.
- CBA mice are commonly used in auditory research because their cochlear structure and their responses to acoustic stimulation closely resemble those of humans. They also tend to exhibit minimal age-related hearing loss, making them reliable models for long-term audiological studies.
- The authors observed that noise exposure did not damage either the outer hair cells or the inner hair cells, as hearing thresholds recovered fully to baseline.
- However, they reported a **permanent loss of presynaptic ribbons**—specialised structures in the inner hair cells responsible for releasing neurotransmitter to activate auditory nerve fibres.

- This permanent loss is illustrated in this graph, where the number of presynaptic ribbons is shown to decrease by approximately 50% at high frequencies after noise exposure, with no recovery observed after 8 weeks.

- Given that the lifespan of a CBA mouse is around 100 weeks, an 8-week follow-up corresponds to roughly seven human years, which is more than sufficient to assess potential recovery.

- The loss of synaptic ribbons led to a persistent reduction in wave I amplitude at supra-threshold levels, with no improvement over time.

- Subsequently, Song et al. (2016) reported that synaptic ribbon loss partially recovers in guinea pigs, highlighting inter-species differences in the vulnerability of the auditory system to noise exposure.

Does cochlear synaptopathy exist in humans?

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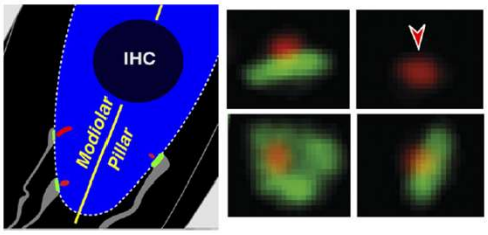

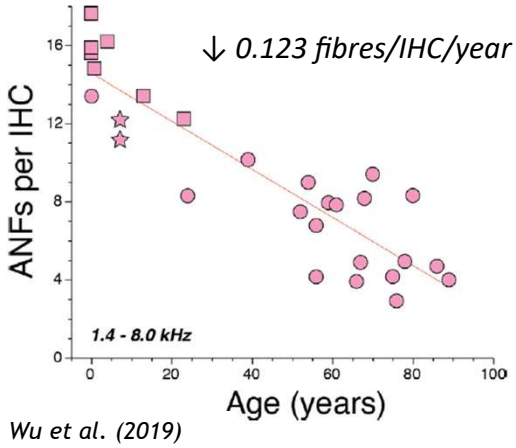

Wu et al. (2019)

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- Cochlear synaptopathy can be measured using confocal microscopy techniques, in which presynaptic ribbons are stained one colour (red in this case) and postsynaptic terminals another (green). This allows researchers to investigate whether cochlear synapses are intact or whether orphaned ribbons (synaptopathy) are present.

- This technique is invasive and can only be used in animal studies, making it currently impossible to determine non-invasively whether cochlear synaptopathy exists in living humans.

- However, histological studies of the temporal bone in post-mortem autopsies show that humans lose approximately 0.123 auditory nerve fibres per IHC per year, demonstrating that cochlear synaptopathy does occur in humans as a result of ageing.

Noise-induced cochlear synaptopathy

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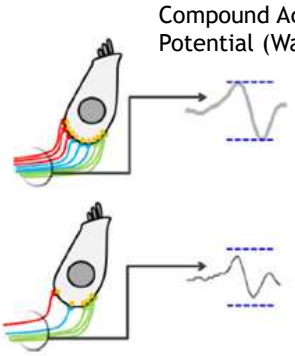
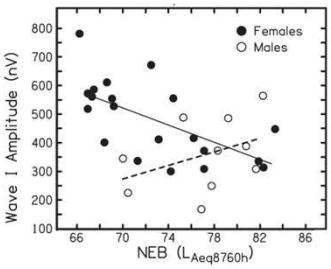
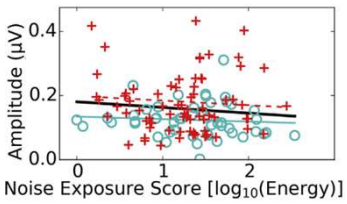




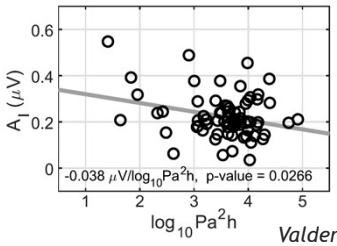
Stamper and Johnson (2015)



Prendergast et al. (2017)

Hypothesis 1: The incidence of CS in humans is negligible

- Different susceptibility to noise in humans
  - Mice (100 dB SPL, 2h), rats and Guinea pigs (106 dB, 2h), Monkeys (108 dB SPL, 4 h), humans (unknown)
- Different noise exposure (continuous vs intermittent)
- Possible recovery from cochlear synaptopathy



Valderrama et al. (2018)

Hypothesis 2: The click-evoked ABR Wave I amplitude is not a sensitive biomarker

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- We have discussed that there is solid evidence that cochlear synaptopathy exists in humans as a result of ageing, but what about noise exposure?

- This aspect is less clear. Studies attempting to relate cumulative noise exposure to Wave I amplitude are inconclusive. For example:
  - Stamper and Johnson (2015) observed a correlation, but only in women.
  - Prendergast et al. (2017) found no relationship.
  - In our own data, we observed a statistically significant correlation, but with high variability, making it impossible to use Wave I amplitude to reliably predict noise exposure.

- This variability leads to two possible interpretations:
  - Noise-induced synaptopathy exists, but wave I is not a good biomarker.
  - The incidence of noise-induced cochlear synaptopathy in humans is minimal. Both interpretations have supporting arguments.

- On the one hand, it is possible that there is actually very little noise-induced cochlear synaptopathy in humans, partly because humans may have different

susceptibility to noise compared with other species studied in the literature. In mice, 100 dB SPL for 2 hours is used to induce synaptopathy; in rats and guinea pigs, 106 dB SPL for 2 hours; in monkeys, 108 dB SPL for 4 hours. In humans, this is unknown. Perhaps the noise exposure we experience is not sufficient to induce cochlear synaptopathy.

- It is also important to note that human noise exposure is very different from that of animals, being intermittent and fluctuating, unlike the single, continuous exposures used in animal studies.

- It could be that, even if the noise we are exposed to causes synaptopathy, we recover between exposures.

- An alternative explanation is that cochlear synaptopathy does exist in humans, but the click-evoked ABR wave I is not sensitive enough.

- I will present five hypothesis that could lead to a more sensitive biomarker.

The high inter-subject variability

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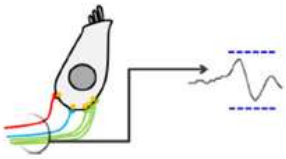
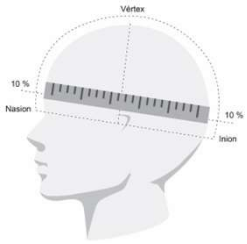
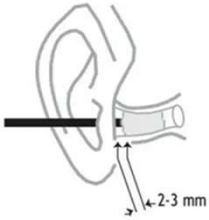
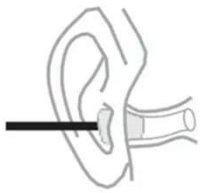


- Auditory nerve fibres (*cochlear synaptopathy*)

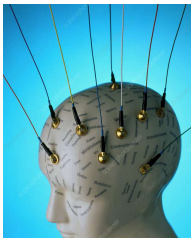


- Head size
- Skull thickness





- Ear canal volume
- Transducer fitting



- Electrode impedance *(signal quality)*

Strategies to reduce inter-subject variability

- Measure anatomic covariables (head size, ear canal volume)
- Ensure the ear-tip fitting is consistent across participants
- Real-ear measures to ensure equal SPL delivered to the eardrum
- Stratify the population by narrow-age groups and gender
- Use a large number of repetitions → High quality recordings
- Get relative measures between individuals → Cancel static factors

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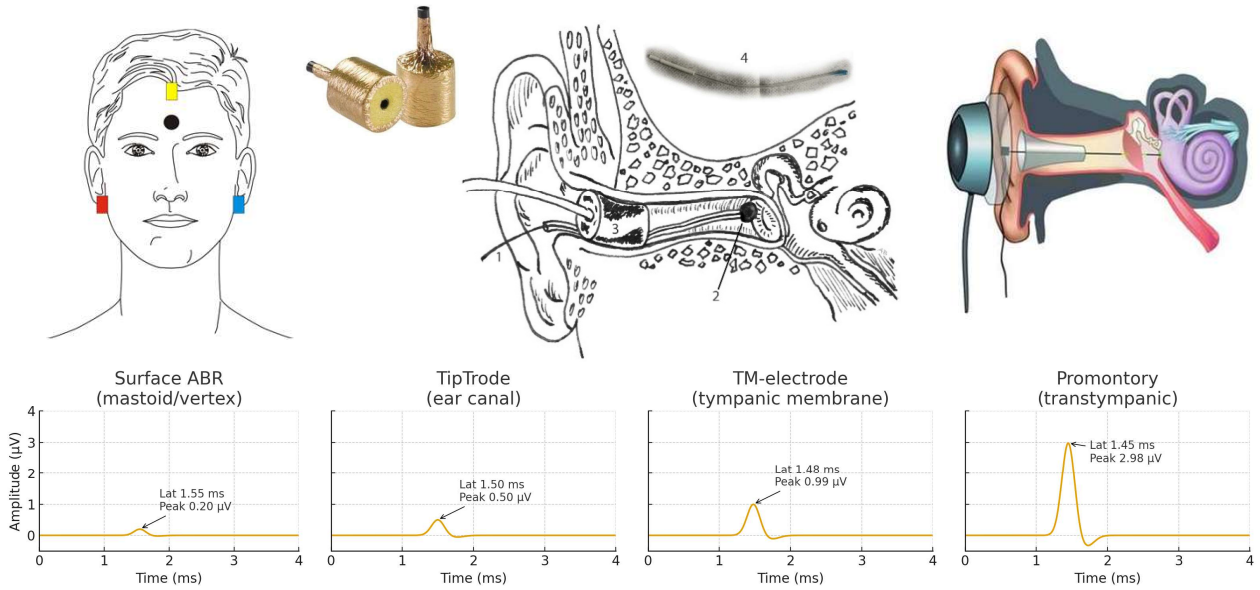
- The amplitude of the compound action potential (wave I of the ABR) shows high inter-subject variability, as we have seen in the previous figures.
- This variability arises because the measure is influenced by a large number of factors.
- In addition to the number of activated auditory nerve fibres (an indicator of possible cochlear synaptopathy), the measure depends on head size (a larger head circumference places the electrodes further from the neural generators, resulting in smaller recorded amplitudes; this is why women typically show larger amplitudes).
- Skull thickness can also distort the electromagnetic fields picked up by the electrodes.
- The volume of the ear canal — particularly the residual volume between the insert earphone and the tympanic membrane — also plays a role: poor earphone placement can increase this volume, reducing the sound pressure level at the eardrum and therefore reducing amplitude.

- Electrode–skin contact impedance likewise affects the measure, as higher impedance increases noise levels and consequently introduces bias.

- To minimise the impact of these variables and isolate as far as possible the contribution of the auditory nerve fibres (which is what we are interested in), I propose a series of strategies.

The low amplitude of the ABR wave I



- Another limitation of the standardised measure is the typically low amplitude of the ABR wave I.
- The figure below shows a simulated example (not an actual recording) illustrating a typical amplitude of around 0.2 μV, obtained using a vertical montage with Fz referenced to the ipsilateral mastoid.
- One strategy to increase the magnitude of the response is to use TIPtrode electrodes, which are placed in the ear canal. Because they are closer to the neural generator (the cochlea), wave I exhibits a larger amplitude, of approximately 0.5 μV.
- An even better approach is to place the electrode directly on the tympanic membrane, which can yield amplitudes of up to 1 μV.
- Ideally, to obtain very large amplitudes, one would place the electrode on the promontory using a transtympanic electrode, with typical amplitudes around 3 μV; however, this method is invasive and therefore not justified for use in normal-hearing individuals without auditory pathology.

The frequency-specificity of CS

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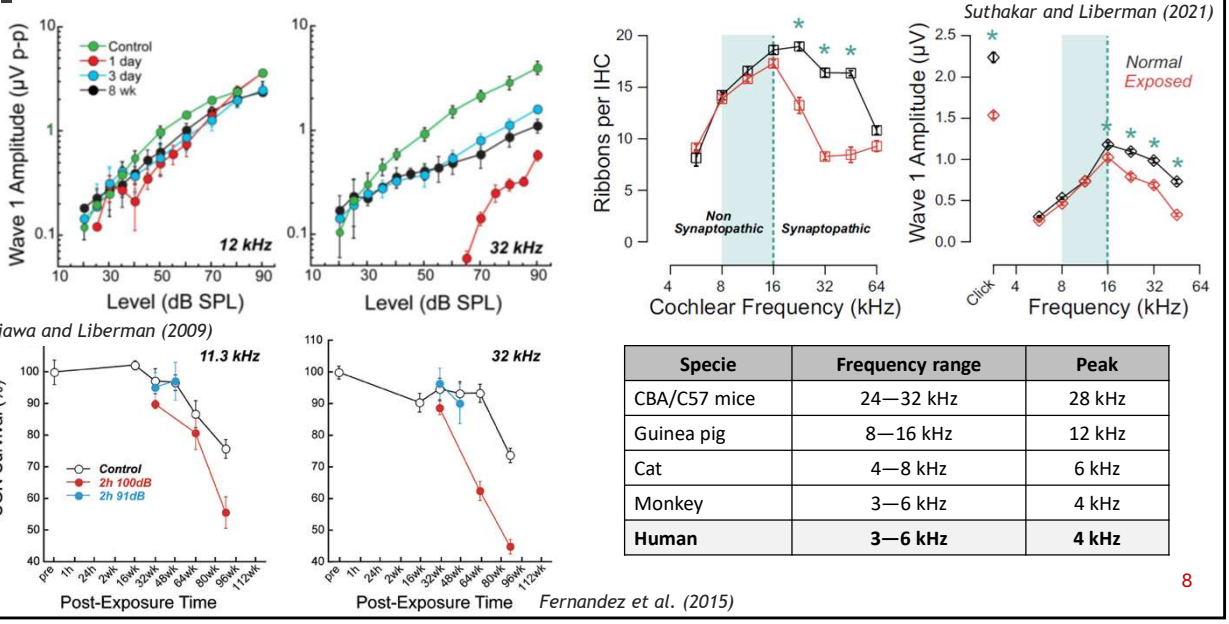

Specie	Frequency range	Peak
CBA/C57 mice	24—32 kHz	28 kHz
Guinea pig	8—16 kHz	12 kHz
Cat	4—8 kHz	6 kHz
Monkey	3—6 kHz	4 kHz
Human	**3—6 kHz**	**4 kHz**

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Fernandez et al. (2015)

- Another strategy to increase the sensitivity of the measure is to use frequency-specific auditory stimuli. This hypothesis is supported by animal studies showing that cochlear synaptopathy is frequency-selective.
- For instance, in Kujawa and Liberman (2009), reductions in supra-threshold wave I amplitude in mice were observed at 32 kHz but not at 12 kHz.
- In Suthakar and Liberman (2021), it was also shown in mice that the loss of presynaptic ribbons occurred only at frequencies above 16 kHz, and that the reduction in wave I amplitude was restricted to cochlear regions where ribbon loss was present.
- Finally, Fernández et al. (2015), who examined the effects of ageing in mice, found that the additional loss of auditory nerve neurons associated with noise exposure was greater in the 32-kHz cochlear region than at 11.3 kHz.
- These findings are consistent with earlier studies identifying the frequency range and peak frequency most susceptible to noise exposure across different species.

- In mice, the most vulnerable cochlear region lies between 24 and 32 kHz, with a peak at 28 kHz; in guinea pigs, between 8 and 16 kHz, peaking at 12 kHz; in cats, between 4 and 8 kHz, with a peak at 6 kHz; and in monkeys, between 3 and 6 kHz, peaking at 4 kHz. Similarly, in humans, the most noise-sensitive region spans 3 to 6 kHz, also with a peak at 4 kHz.

The frequency-specificity of CS

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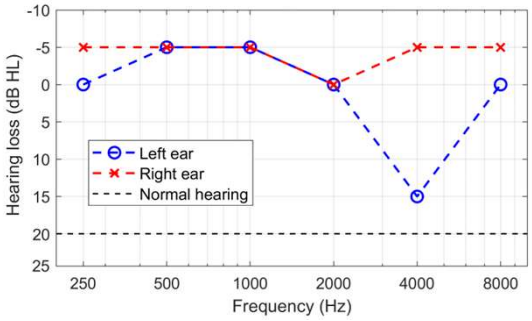
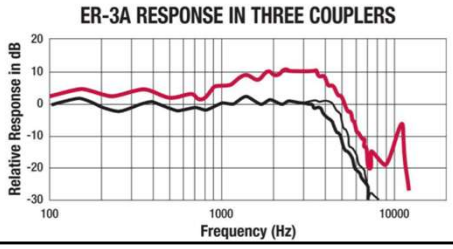
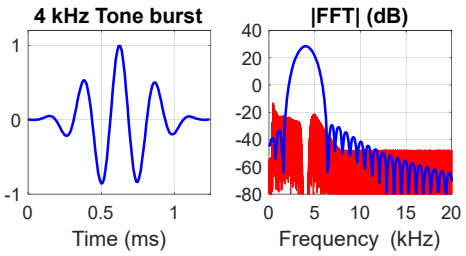




- Vascular and metabolic vulnerability
- High amplitude of the cochlear traveling wave
- A differential change in attachment and stiffness in the Basilar membrane basal turn
- Ear-canal resonance (amplify 3—6 kHz)

- Click-ABR → cochlear activity from the 2—6 kHz region
  - Apical region (lower frequencies) is desynchronised
  - ER-3A transducer reduce frequencies above 6 kHz



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- Hence, in humans, noise exposure often results in the well-known 4-kHz notch. This audiogram is, in fact, my own, showing a notch of about 15 dB at 4 kHz (while still within the range of clinically normal hearing).

- Several explanations have been proposed for the high susceptibility of the 4-kHz cochlear region.

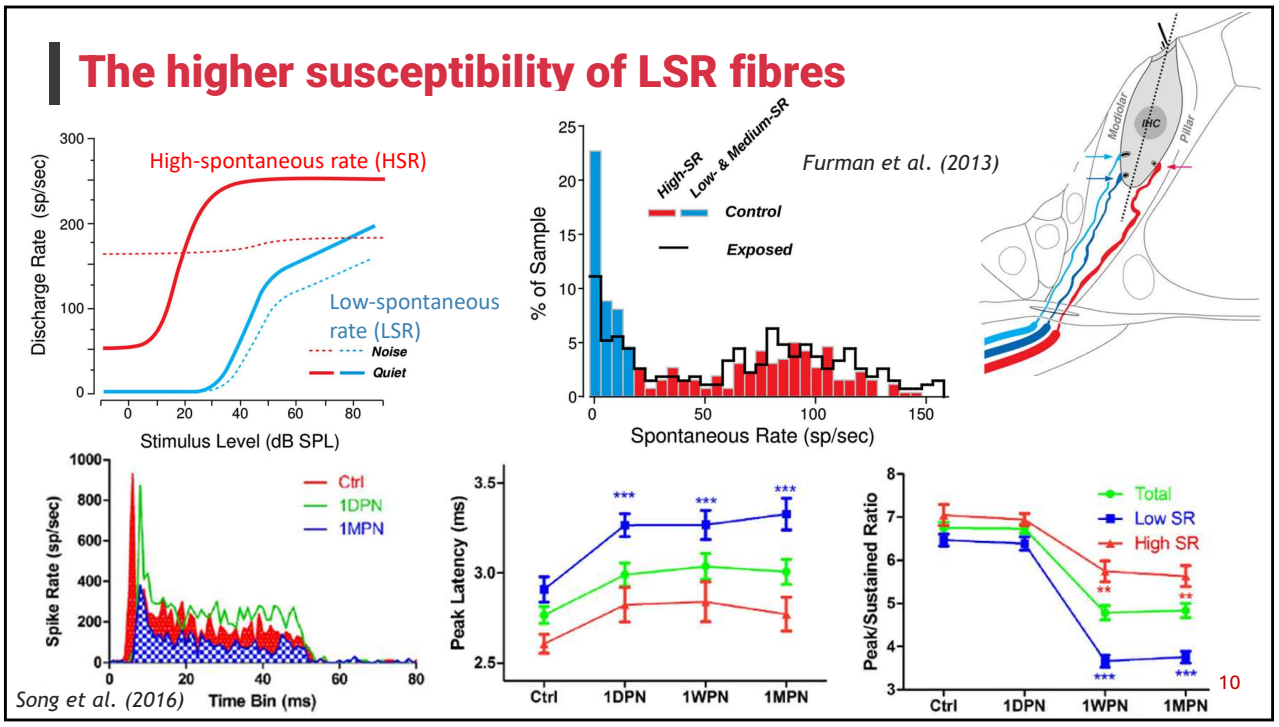
- These include vascular and metabolic factors; the fact that the travelling wave reaches its maximum amplitude in this region; the possibility of a rapid change in basilar-membrane stiffness or in its anchoring to the bony structure; and the resonance of the ear canal, which amplifies sounds in the 3–6 kHz range.

- Importantly, if cochlear synaptopathy in humans is concentrated around 4 kHz, ABRs evoked by clicks may not be sufficiently specific, as they reflect activity from a broader cochlear region—potentially including areas unaffected by synaptopathy.

- Clicks primarily stimulate the 2–6 kHz region of the cochlea. Low frequencies

contribute little because the travelling-wave delay to the apical region causes neural responses to become desynchronised with the stimulus, and frequencies above 6 kHz are attenuated due to the characteristics of the transducer (commonly the ER-3A).

- Taking these considerations into account, we propose that a 4-kHz-centred tone burst combined with TEN noise containing a 4-kHz notch filter may provide an optimised stimulus to target the cochlear region most likely to exhibit synaptopathy in humans.



- An important aspect of cochlear synaptopathy is that it appears to be selective for low spontaneous rate fibres.

- Each inner hair cell (IHC) is innervated by around 15 auditory nerve fibres. Animal studies have shown that not all fibres are the same; they can be categorised according to their spontaneous rate, that is, their firing rate in the absence of a stimulus.

- The red trace in the figure on the left shows the firing rate of a high spontaneous rate fibre: we can see that for 0 dB SPL stimuli, it exhibits a high spontaneous rate. In the presence of background noise, the firing rate of these fibres saturates, so they are believed not to contribute to the encoding of information in noisy environments, such as a café or restaurant.

- By contrast, low spontaneous rate fibres (blue trace) are more robust in the presence of noise—we can see that they do not saturate—so these fibres are thought to play a critical role in understanding speech in noisy situations.

- The study by Furman et al. (2013) compared the percentage of high- and low-

spontaneous rate fibres in guinea pigs with and without noise exposure, observing that loss occurred only in low spontaneous rate fibres—the very fibres responsible for neural coding of information in noisy environments.

- Another significant development was the discovery that cochlear synaptopathy does not affect only low–spontaneous rate (LSR) fibres; high–spontaneous rate (HSR) fibres are also affected, although to a lesser extent.

- The study by Song et al. (2016) in guinea pigs analysed the firing rates of these neurons in response to a 50-ms stimulus using peri-stimulus time histograms.

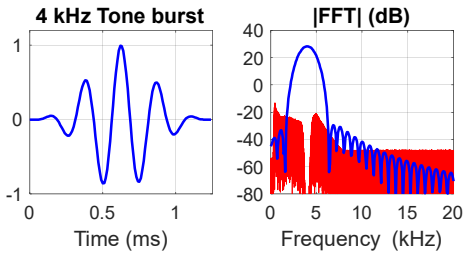
- Noise exposure produced an increase in peak latency in both fibre types, although the effect was more pronounced in LSR fibres.

- When examining the ratio between the onset peak firing rate and the sustained response, it again became evident that noise exposure affects both fibre types, but with a larger impact on LSR fibres.

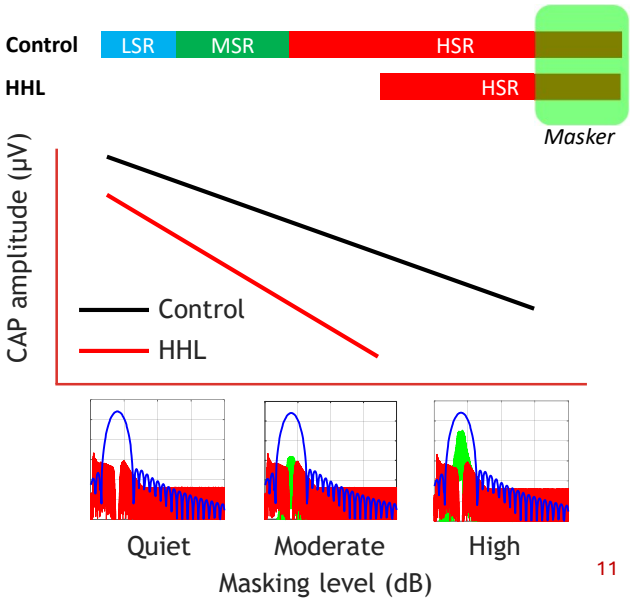
- These findings show that noise exposure does not exclusively affect LSR fibres, as suggested by the classical model, but also impacts high–spontaneous rate fibres. Nevertheless, the effects of cochlear synaptopathy—and the degree of incomplete recovery—appear to be greater in LSR fibres.

- A further strong argument indicating that cochlear synaptopathy does not affect only LSR fibres is that, assuming a typical distribution of around 15% LSR fibres (Liberman, 1978), the ~50% loss of synapses reported by Kujawa and Liberman (2009) would necessarily affect not only LSR fibres but also fibres with higher spontaneous rates.

ECochG – experiment 1



- **Stimulus**: 4 kHz *Tone burst* at 90 dB SPL (to activate LSR fibres) on notched TEN noise at 60 dB SPL (to isolate the region of interest).
- **Masker**: 4 kHz band-pass noise at different SNRs (to mask different fibre groups).
- **Stimulus rate**: Low (~10 stim/s) to minimise adaptation.
- **Electrode**: TM-electrode.



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- Taking these considerations into account, we have designed an ECochG experiment aimed at assessing the loss of LSR fibres through the amplitude of the compound action potential.
- In this experiment, we will use the frequency-specific stimulus described earlier: a 4-kHz tone burst presented in TEN noise with a notch.
- We will then evaluate the reduction in CAP amplitude as we increase the level of a narrowband masking noise centred on the frequency region of interest (4 kHz).
- Our hypothesis is that, in an extreme scenario in which individuals with HHL have lost around 50% of the higher-threshold fibres, their CAP amplitude in quiet (i.e., without masking noise) will be smaller due to the reduced number of active fibres.
- Crucially, as the level of the masking noise increases, HSR fibres will saturate rapidly, and because these individuals lack the higher-threshold LSR fibres, their CAP amplitude will decline more steeply.

- The experiment will be conducted using low stimulation rates to ensure that neural adaptation does not affect the amplitude of the response, and we will place the electrode on the tympanic membrane to obtain recordings with the highest possible amplitude.

The higher resilience of LSR fibres

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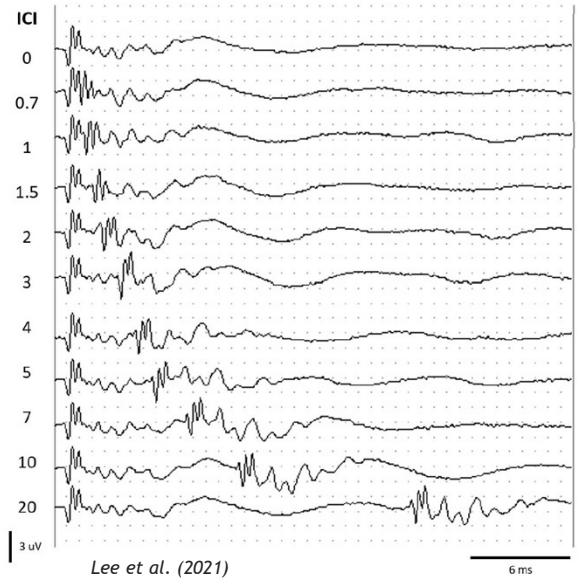
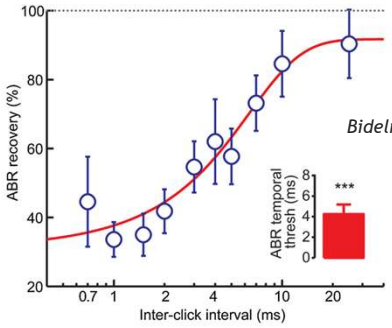


Lee et al. (2021)



Bidelman and Khaja (2014)

	HSR	LSR
Threshold	Low	High
Firing probability	Very high	Low
Vesicle release saturation	Rapidly saturates after first stimulus	Maintain a larger vesicle reserve

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- The paired-click stimulation paradigm has been used to assess the temporal resolution of the peripheral auditory system.
- This paradigm involves recording ABR signals evoked by a set of click pairs separated by a variable inter-click interval (ICI).
- The relationship between the recovery of the ABR to the second click relative to the first click provides information about temporal resolution.
- Recovery is defined as the percentage amplitude of the second click relative to that of a single click (ICI = 0 ms).In humans, the greatest suppression occurs at ICIs of around 1 ms, and full recovery is typically achieved at an ICI of 20 ms.
- The hypothesis behind this paradigm is that LSR fibres have a higher activation threshold than HSR fibres, such that the first click activates the HSR fibres, but is not sufficient to activate the LSR fibres (leaving presynaptic vesicles available for encoding).

- Therefore, the rapid presentation of a second click becomes an indicator of the integrity of LSR fibres.

- Reduced recovery indicates that no LSR fibres are available to encode the information from the second click, and this effect becomes more pronounced as the ICI decreases.

The higher resilience of LSR fibres

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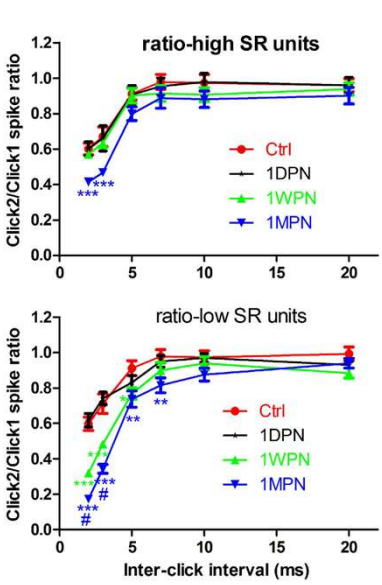
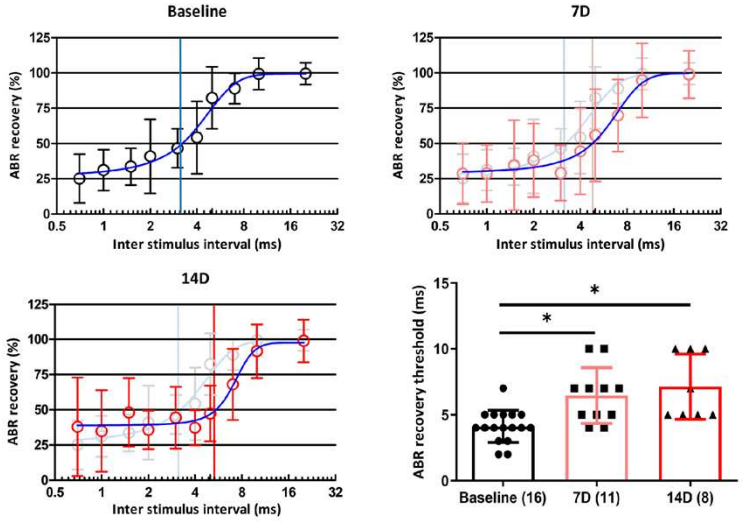


Song et al. (2016)



Lee et al. (2021)

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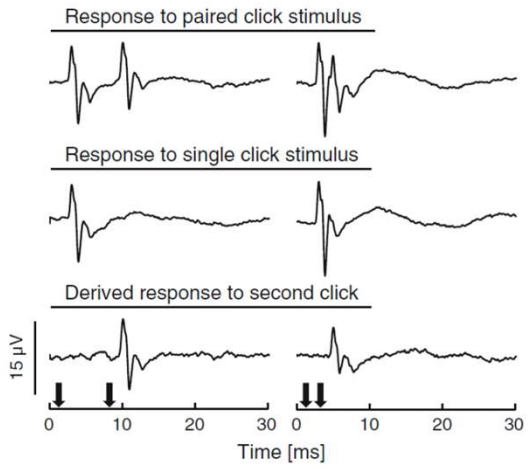
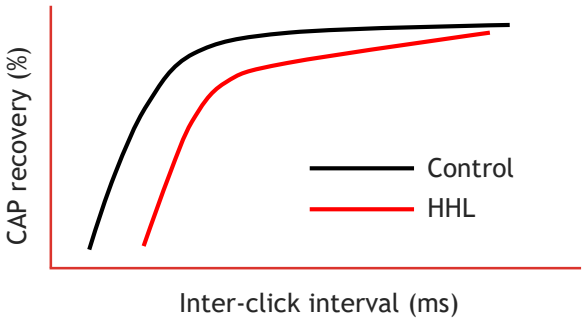
- This effect has indeed been observed in animal studies.
- In guinea pigs, it was found that recovery ability—measured as the firing-rate ratio of click 2 to click 1—was reduced in HSR fibres of noise-exposed animals, and that this recovery capacity was reduced even further in LSR fibres. This is consistent with the central message of that study: noise exposure affects both HSR and LSR fibres, but with a larger impact on LSR fibres.
- In the study by Lee et al. (2021) in rats, the authors observed that the recovery threshold, measured as the ICI resulting in 50% recovery, increased following noise exposure.
- These results indicate that the recovery of CAP amplitude at short inter-stimulus intervals may serve as a potential biomarker of cochlear synaptopathy.

ECochG – experiment 2



- Paired click paradigm → highly inefficient
- ABR at fast presentation rates via **deconvolution**
- **Stimulus**: 4 kHz *tone burst* on notched TEN noise nivel medio (90 dB ppeSPL) para que activen HSR fácilmente, pero LSR solo parcialmente.
- **ICI**: 4 ms (fast rates) – 6 ms – 8 ms – 10 ms – 100 ms
- **CAP recovery**: relative to the ICI=100 ms condition



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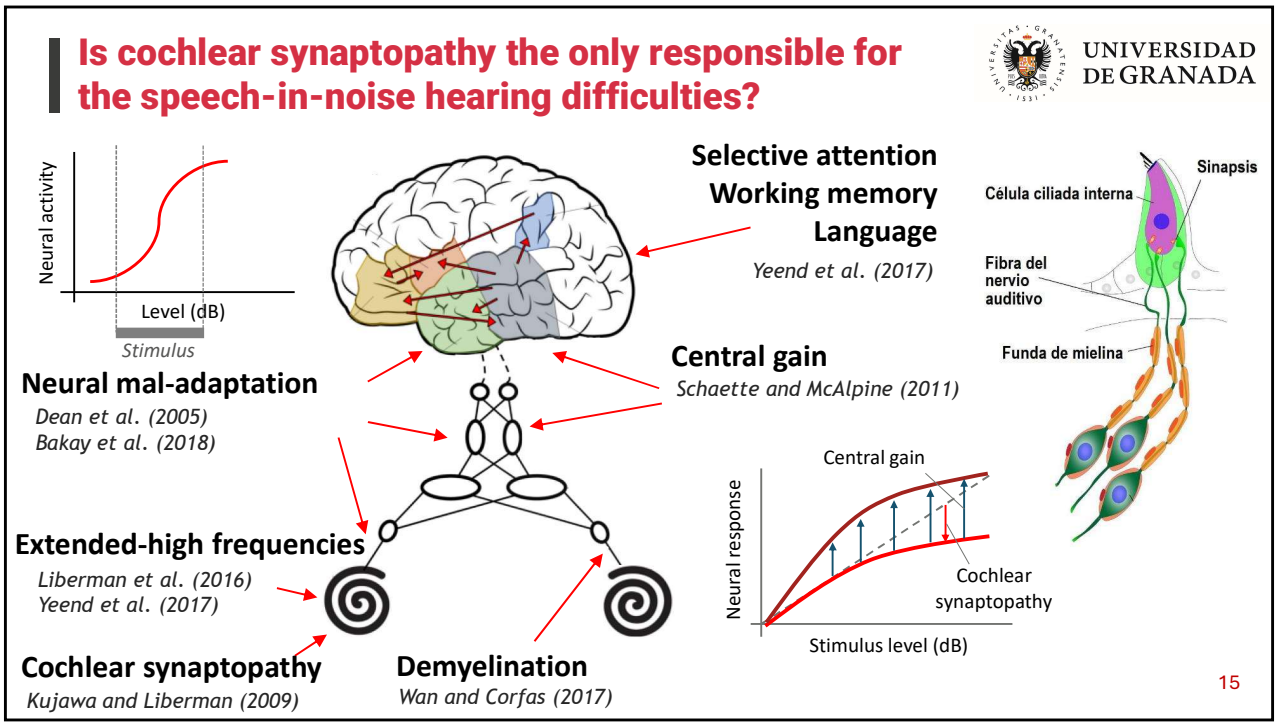
- The left-hand panel illustrates the estimation of the CAP morphology to the second click, which is 'contaminated' by the first.
- The response to the first click is subtracted based on an isolated-click recording, and the residual is attributed to the second click, akin to a simple deconvolution.
- The paired-click paradigm is highly inefficient due to the long inter-pair intervals required.
- This approach can be substantially improved by recording CAPs at high stimulation rates and estimating morphology using contemporary deconvolution techniques.
- We will again employ a 4 kHz tone burst in TEN noise with a 4 kHz notch, at variable rates ranging from low (10/s) to high (mean ICI of 4 ms), hypothesising that individuals with hidden hearing loss will exhibit poorer CAP recovery at high stimulation rates.



- People with hidden hearing loss do not complain of having cochlear synaptopathy per se, but rather of difficulty following conversations with family or friends in restaurants, cafés, or noisy environments. Cochlear synaptopathy is a possible cause of these difficulties, but it is not the only one.

- Elevated thresholds at frequencies above those typically measured in the clinic (10–16 kHz) are considered an indicator of early hearing loss symptoms that negatively affect speech understanding in noise.

- Demyelination occurs when the myelin sheath surrounding the auditory nerve is altered. This myelin sheath accelerates the propagation of impulses along the auditory nerve axon, and its alteration can affect binaural hearing, which plays an important role in source segregation and listening in noisy situations.

- Central gain mechanisms occur at central stations as a consequence of peripheral alterations. Following cochlear synaptopathy, neurons have difficulty encoding loud sounds, so more central neural stations increase their sensitivity to cover the full dynamic range.

- Additionally, Dean and colleagues discovered that neuronal activity patterns adapt to the statistics of sound to optimise neural coding of those sounds. Bakay et al. (2018) found that animals with synaptopathy lost this neuronal adaptation ability.

- Beyond these neural encoding processes, understanding a message requires a range of central cognitive processes. In particular, working memory, language proficiency, and selective attention are important. Selective attention refers to the ability to focus on the target sound source while inhibiting other distracting sources (for example, conversations at neighbouring tables in a noisy restaurant).

Study groups

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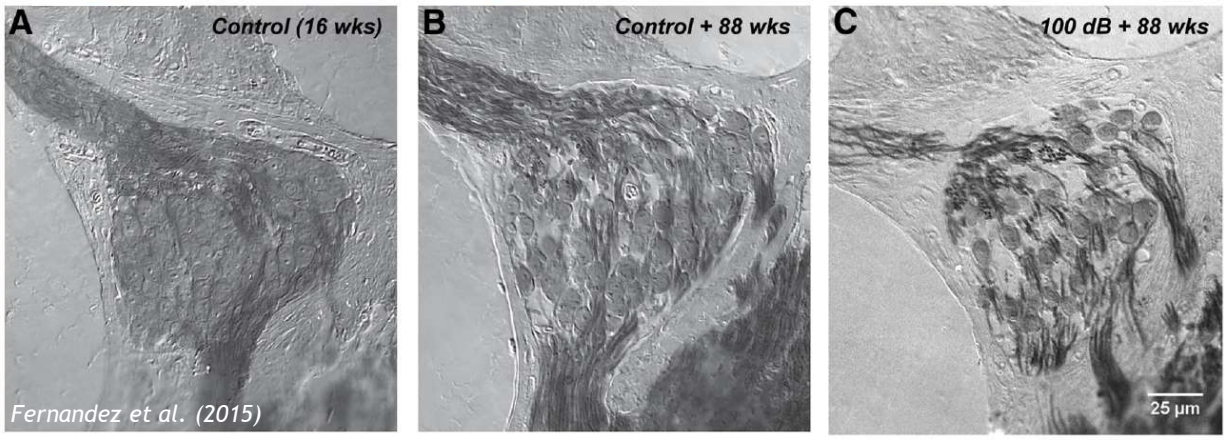
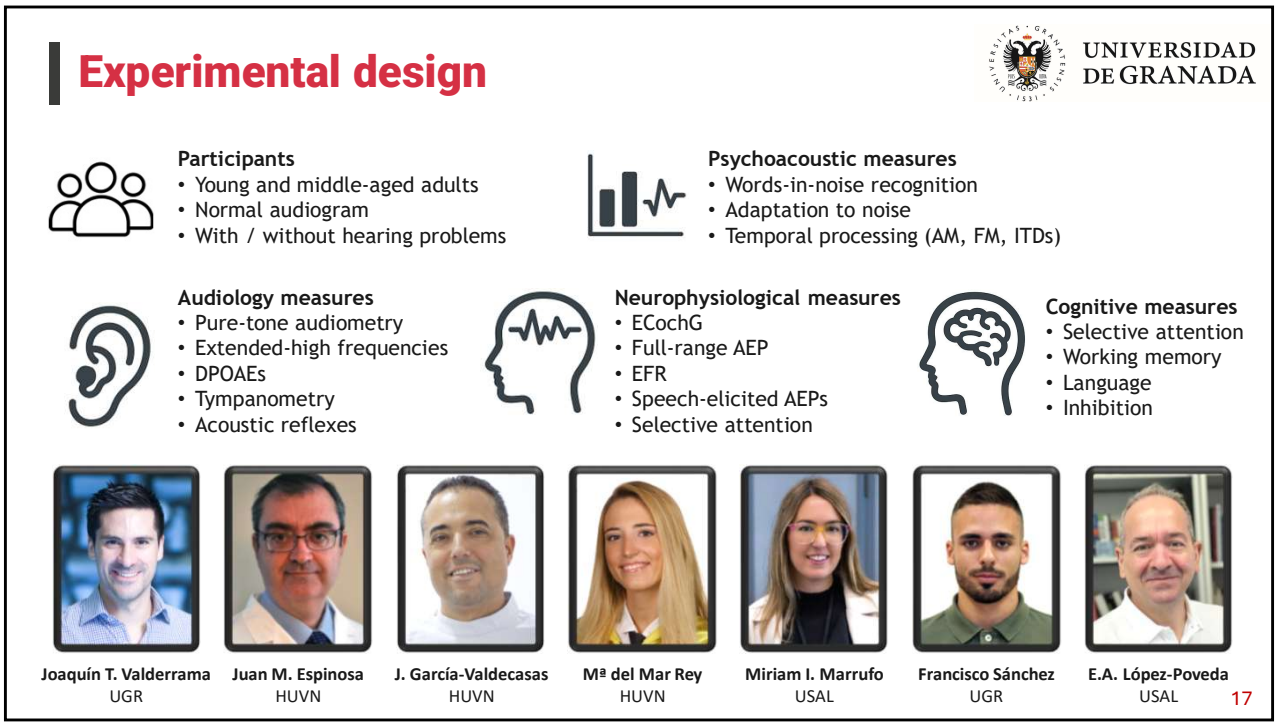
Young - Low noise
- 18–25 years
- Low noise exposure
- No HHL

Mid-age - Low noise
- 45-55 years
- Low noise exposure
- Age-related HHL

Mid-age - High noise
- 45-55 years
- High noise exposure
- Age- & noise-HHL



- We considered three groups of participants, all with clinically normal audiograms.
- The first comprised young adults with minimal noise exposure and no auditory difficulties, expected to have no hidden hearing loss (HHL).
- The second group included middle-aged adults (45–55 years) with low noise exposure and no major hearing complaints, expected to exhibit some age-related HHL.
- The third group consisted of middle-aged adults of the same age range with high noise exposure, expected to show HHL associated with both age and noise.
- This grouping was inspired by Fernandez et al. (2015), who assessed spiral ganglion neuron integrity in young mice, aged mice, and aged mice exposed to noise, demonstrating that noise exposure accelerates ageing similarly to how sun exposure accelerates skin ageing.



- To measure this ecosystem of variables, our research team is currently designing a battery of measures potentially sensitive to auditory pathologies believed to underlie the speech-in-noise comprehension difficulties reported by individuals with normal audiometric thresholds.

- The test battery includes audiological, psychoacoustic, neurophysiological, and cognitive measures. I do not have time today to describe all these measures in detail, although I hope that at the next edition of this conference I will be able to share preliminary results from this study that will shed light on the mechanisms involved in hidden hearing loss.

- Before moving on to the main conclusions of my talk, I would like to invite you to take part in the Virtual Conference on Computational Audiology in June 2026, which I am coordinating together with my colleagues Dr María Amparo Callejón Leblic from the Virgen Macarena University Hospital, and Dr Miriam Isabel Marrufo Pérez from the University of Salamanca.

- It is a free online conference, and we will be joined by leading international speakers in the fields of *computational audiology, binaural hearing*, and related areas

- Make sure to save the date!

Conclusions

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- Hidden hearing loss affects a substantial segment of the population, significantly impacting communication in noisy environments.
- Frequency-specific tone bursts in increasing narrow-band masking noise may help reveal the loss of LSR fibres.
- High-rate CAP recordings could increase sensitivity to deficits in LSR fibres, potentially improving detection of cochlear synaptopathy.
- An integrated approach combining peripheral and central measures is proposed to characterise the multifactorial nature of hidden hearing loss.

SLIDES & NOTES

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