

## Electrophysiological evidence of noise-induced cochlear synaptopathy in humans

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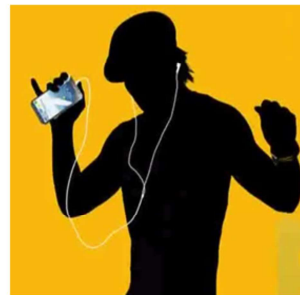
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- Good morning, I am Joaquin Valderrama, from the National Acoustic Laboratories and Macquarie University.
- In this presentation, I will talk about the influence of noise exposure on the human auditory system.
- Before starting, please let me acknowledge the contribution to this work of my colleagues Elizabeth Beach, Ingrid Yeend, Mridula Sharma, Bram Van Dun, and Harvey Dillon.

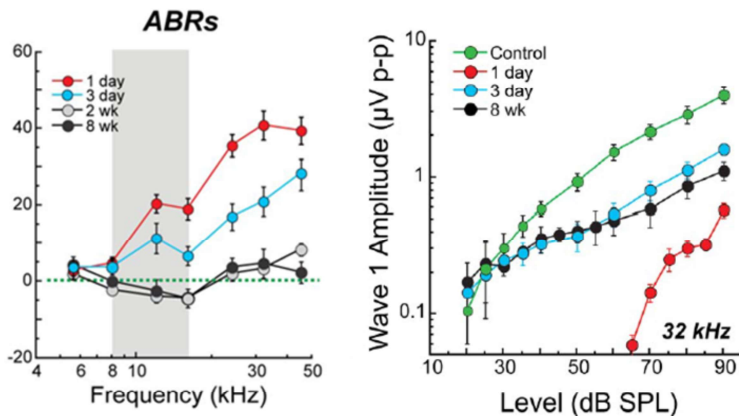
## How dangerous is excessive noise exposure?



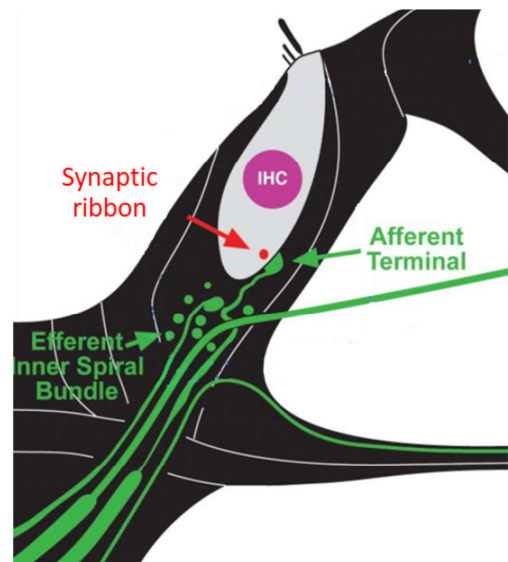
- How dangerous is being exposed to noise?
- In other fields the answer to this question would be straightforward. We know that too much sun exposure, drinking too much alcohol or sedentariness can negatively affect our health.
- For this reason, because we are aware of these damaging effects, we wear sunscreen when we are on the beach, we drink responsibly and we try to workout from time to time.
- What happens with noise exposure? We might have heard that noise exposure can be dangerous, but still we usually attend to loud music venues, and it's usual to find people seated next to us on the train with the volume of the earphones at the maximum level.
- Understanding the effect of noise exposure on our hearing health is key to give adequate prevention messages to the society.
- What do we actually know about the effects of noise exposure?

## Adding Insult to Injury: Cochlear Nerve Degeneration after “Temporary” Noise-Induced Hearing Loss

Sharon G. Kujawa<sup>1,2,3,4</sup> and M. Charles Liberman<sup>1,2,4</sup>



Noise exposure causes cochlear synaptopathy



- In this study, Kujawa and Liberman carried out an animal study in young-healthy anaesthetized mice. They presented filtered noise at 100 dB during 2 hours.
- 100 dB is a loud noise, but it is a level that you could easily find in many leisure activities, such as in a rock concert.
- They found that one day after the test, the ABR thresholds increased (red line, which means that their hearing was worse), but interestingly these thresholds recovered after few weeks.
- This might probably sound familiar to some of us. If we did an audiometry just after a concert, the audiometry would probably reveal that our hearing is worse, but after a few days we feel that our hearing goes back to normality.
- However, what happened next is that when they inspected the auditory nerve of the exposed mice, they observed that noise-exposure led to an irreversible loss of around 50% of the synaptic ribbons, which are responsible for the connection between the IHC and the auditory nerve. In other words, noise exposure was causing cochlear synaptopathy.
- They corroborated this result by comparing the amplitude of the ABR wave I at high

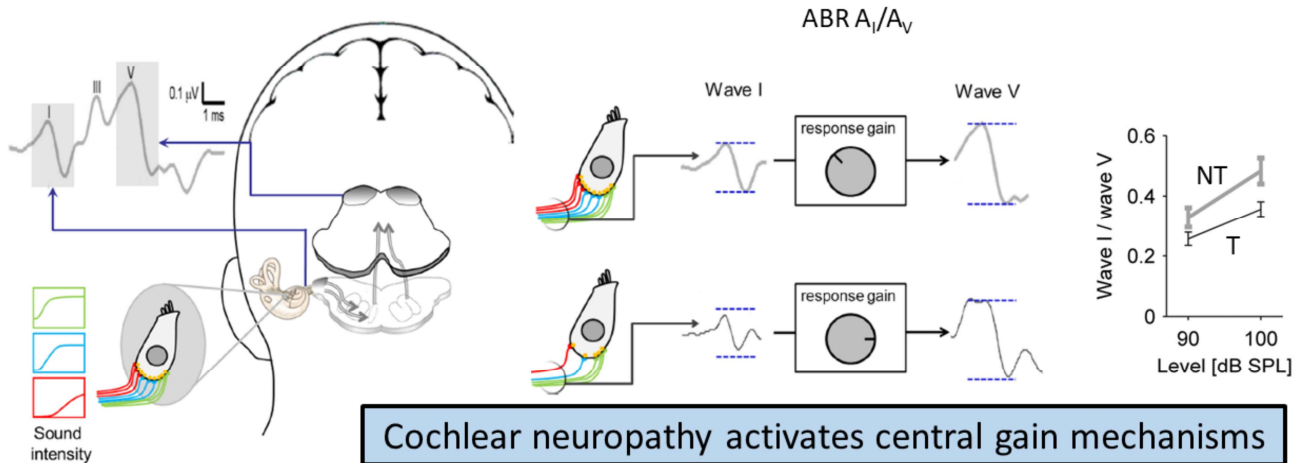
levels. The amplitude of wave I is considered to be an indicator of the amount of ANF activation. They found that noise exposure led to a lower wave I amplitude.

- These results inspired a theory in which many people with problems in understanding speech in noise (SIN) would present a normal audiogram, leading to a hidden hearing loss. Hidden, because there are no tests available to evaluate the state of these type of neurons.

## Tinnitus with a Normal Audiogram: Physiological Evidence for Hidden Hearing Loss and Computational Model

Roland Schaette and David McAlpine

University College London Ear Institute, London WC1X 8EE, United Kingdom



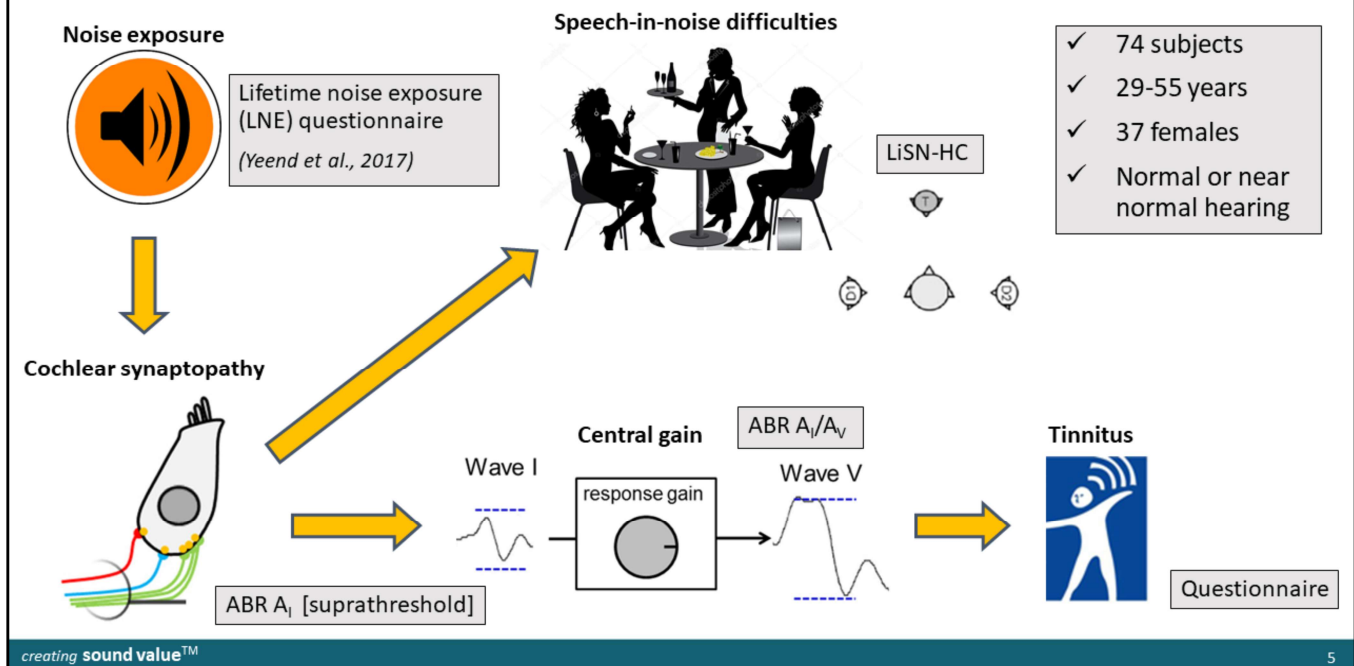
**Cochlear neuropathy activates central gain mechanisms**

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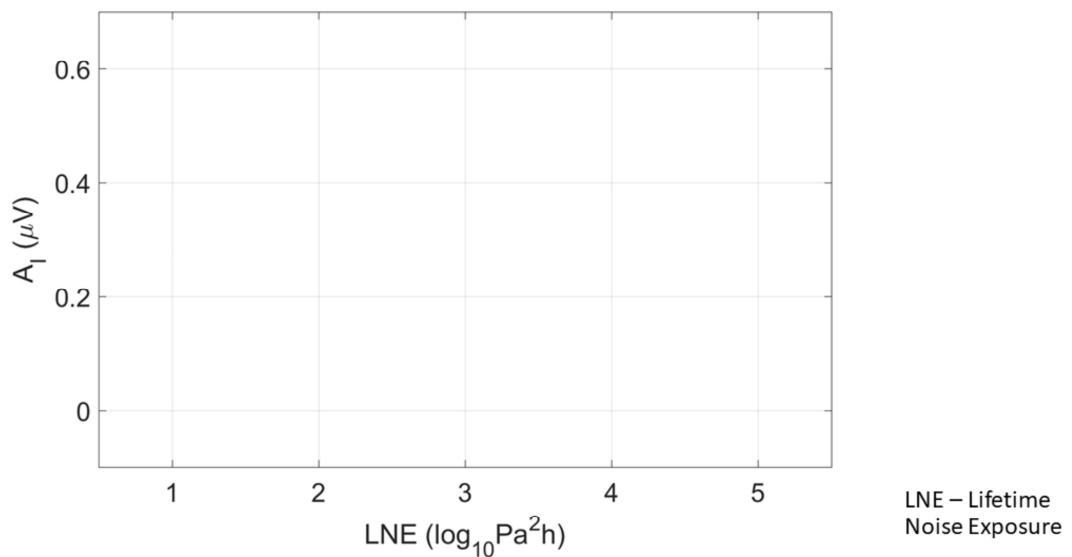
- This was in animals, in humans, Schaette and McAlpine observed the waves I and V as indicators of the state of the neurons in the cochlea and in the midbrain, a more central stage of the auditory pathway.
- Compared to normal hearers, they observed that cochlear damage led to a reduced wave I (as a consequence of less fibres contributing to the response), but equal-amplitude wave V, as a consequence of the activation of central gain mechanisms that compensate the reduced input from the cochlea.
- They provided the ratio of the amplitudes of waves I and V as an indicator of activation of central gain mechanisms
- In particular, they found that subjects reporting tinnitus had reduced ratios of waves I and V, suggesting that tinnitus could be the consequence of the activation of this central gain mechanisms.

## Methods and hypotheses



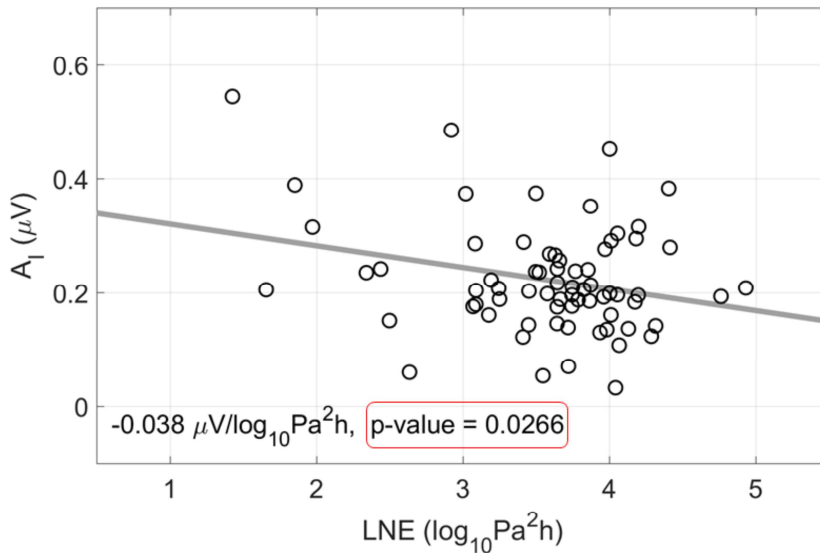
- In order to understand the potential effects of noise on the human auditory system, we hypothesized that (1) noise exposure would cause cochlear synaptopathy, (2) the reduced wave I amplitude resulting from cochlear synaptopathy would be compensated by central gain mechanisms, leading to equal wave V amplitudes, (3) and that this neural reorganization would provoke tinnitus; also, (4) we hypothesized that subjects with cochlear synaptopathy would present a poorer performance in speech-in-noise tests.
- What did we do? We tested 74 subjects in the age range 29-55 years, 37 of them females, who presented normal or near normal hearing as diagnosed in the clinic.
- We evaluated noise exposure with the LNE questionnaire, we evaluated cochlear synaptopathy with the ABR wave I evoked at suprathreshold level, we measured central gain activation by the ratio of waves I and V, we asked the participants about their tinnitus in the same questionnaire, and we evaluated speech-in-noise performance using the LiSN-HC test, in which the participant had to repeat a sentence from a target speaker situated in front, in the presence of two distractors spatially separated 90° from the source.

## Is cochlear synaptopathy present in humans?



- The first research question that we addressed was if cochlear synaptopathy was present in humans.
- To answer this question we correlated the amplitude of wave I, being a low value an indicator of cochlear synaptopathy, and LNE.
- Note that this scale is logarithmic, so 2 means 10 times more noise exposure than 1, 3 means 100 times, 4 means a thousand times more noise exposure than 1, and so on.
- We hypothesized that more noise exposure would lead to a reduced amplitude of wave I.

Is cochlear synaptopathy present in humans?

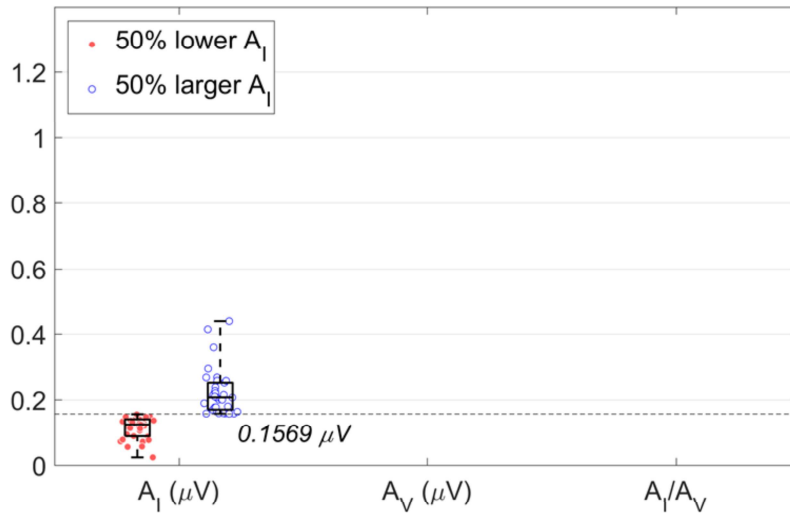


Noise exposure can damage the human cochlea

- Our results showed a statistically significant negative association between the amplitude of wave I and LNE.
- This result is consistent with the cochlear synaptopathy model observed in animal studies, and supports the notion that cochlear synaptopathy might be present in humans.
- This figure also shows that the correlation between these two variables is just moderate. This is probably due to 2 main factors: (1) the way we evaluate LNE through the questionnaire might be subject to a certain amount of human bias and recall errors, [we need to be aware that we are asking the subjects to remember events and hearing routines from a fairly distant past]; and also (2) because the A1 estimate is known to present a large degree of individual variability, depending on other factors like head size.
- Probably because of these two limitations, this figure might show that at a population level noise exposure can damage the human cochlea, and in particular, the synapsis between IHCs and ANFs, but at an individual level, these two measures are clearly insufficient for diagnosis purposes.

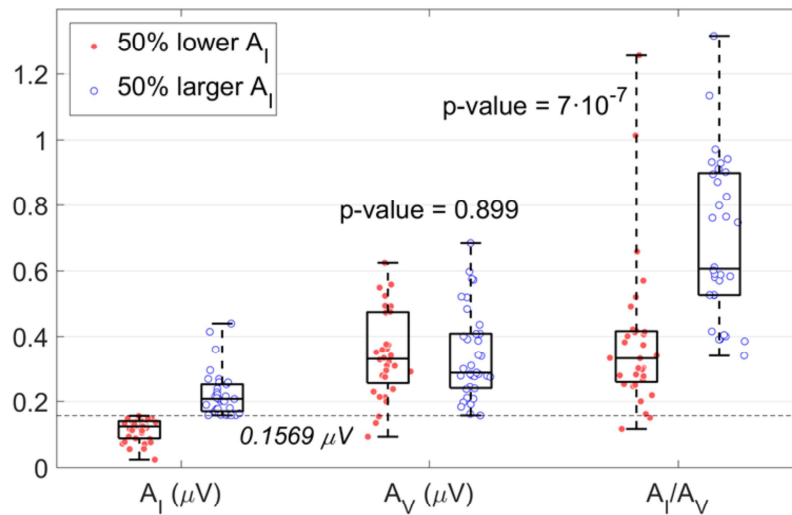


## Does low $A_I$ activate central gain mechanisms?



- We also wondered if reduced wave I amplitudes would be compensated by central gain mechanisms.
- To answer this question, we categorized our subjects according to the amplitude of wave I, and we hypothesized that if central gain mechanisms were active, we would not observe differences in the wave V amplitudes.

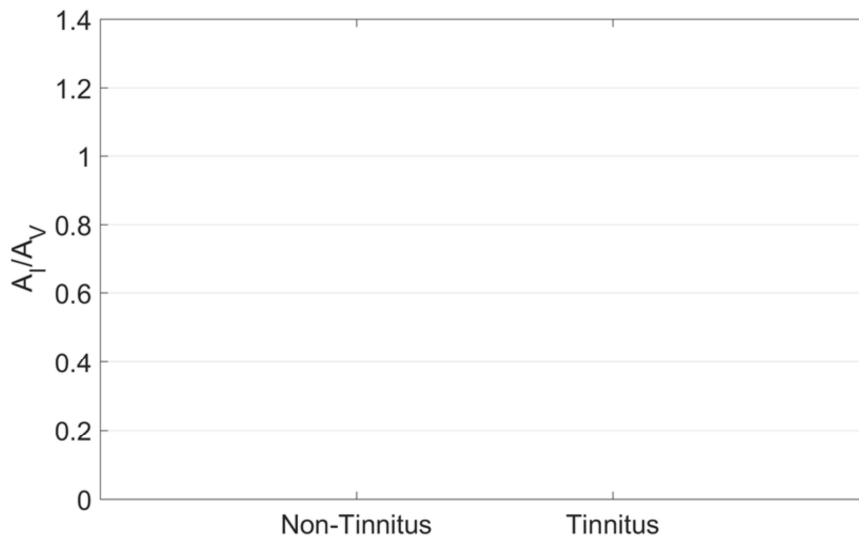
## Does low $A_I$ activate central gain mechanisms?



Central gain mechanisms compensate for a reduced input from the cochlea – low  $A_I/A_V$

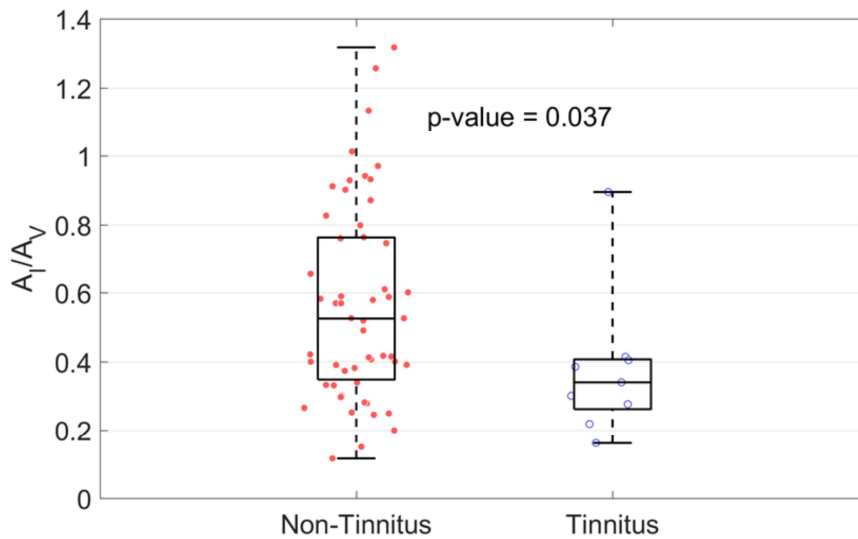
- We observed that, as expected, there were no significant differences between the wave V amplitudes in the two groups.
- As a consequence, the  $A_I/A_V$  ratio was smaller in the group of subjects with reduced wave I, and therefore, the  $A_I/A_V$  ratio remained as an indicator of central gain activation.

Does central gain induce tinnitus?



- We also hypothesized that, if central gain is the cause of tinnitus, subjects reporting tinnitus would show reduced A1 A5 ratios.

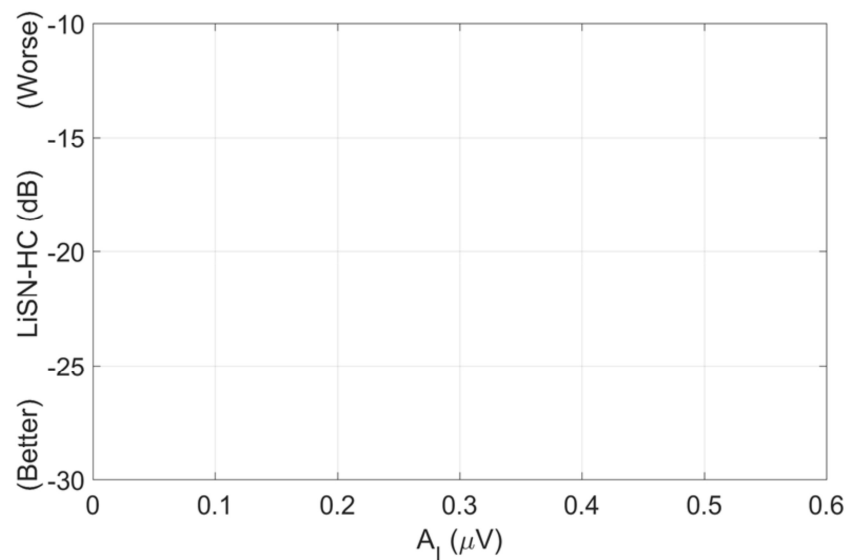
Does central gain induce tinnitus?



Tinnitus is associated with central gain mechanisms

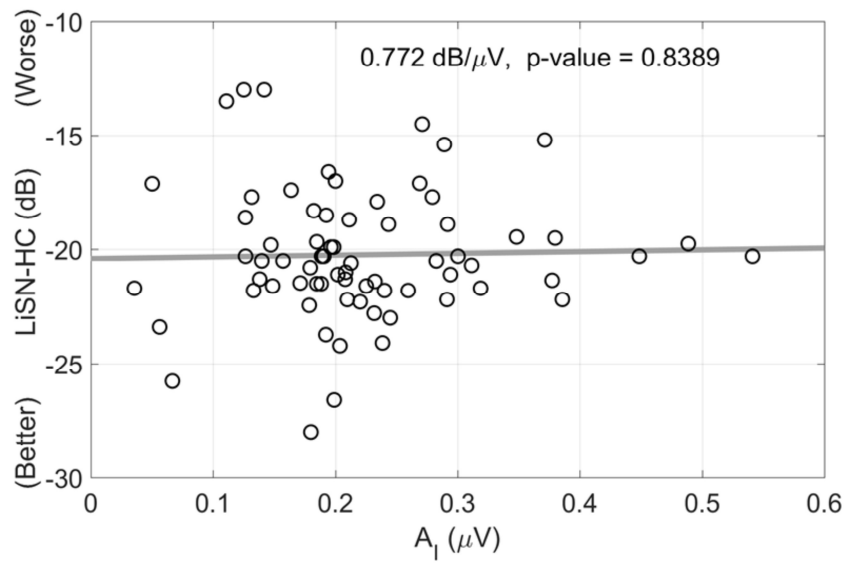
- And indeed, we found that subjects reporting tinnitus frequently or always had reduced A1 A5 ratios compared to those reporting tinnitus 'never', 'sometimes' or 'occasionally'.
- This result supports the theory in which tinnitus is a consequence of central gain activation.

## Is there a link between cochlear synaptopathy and SIN difficulties?



- Finally, we investigated a direct relationship between cochlear synaptopathy and speech-in-noise difficulties.
- To do this, we correlated the amplitude of wave I and the score on the LiSN-HC test, in which a lower threshold indicates better SIN performance.
- We expected to find a negative association between these two variables.

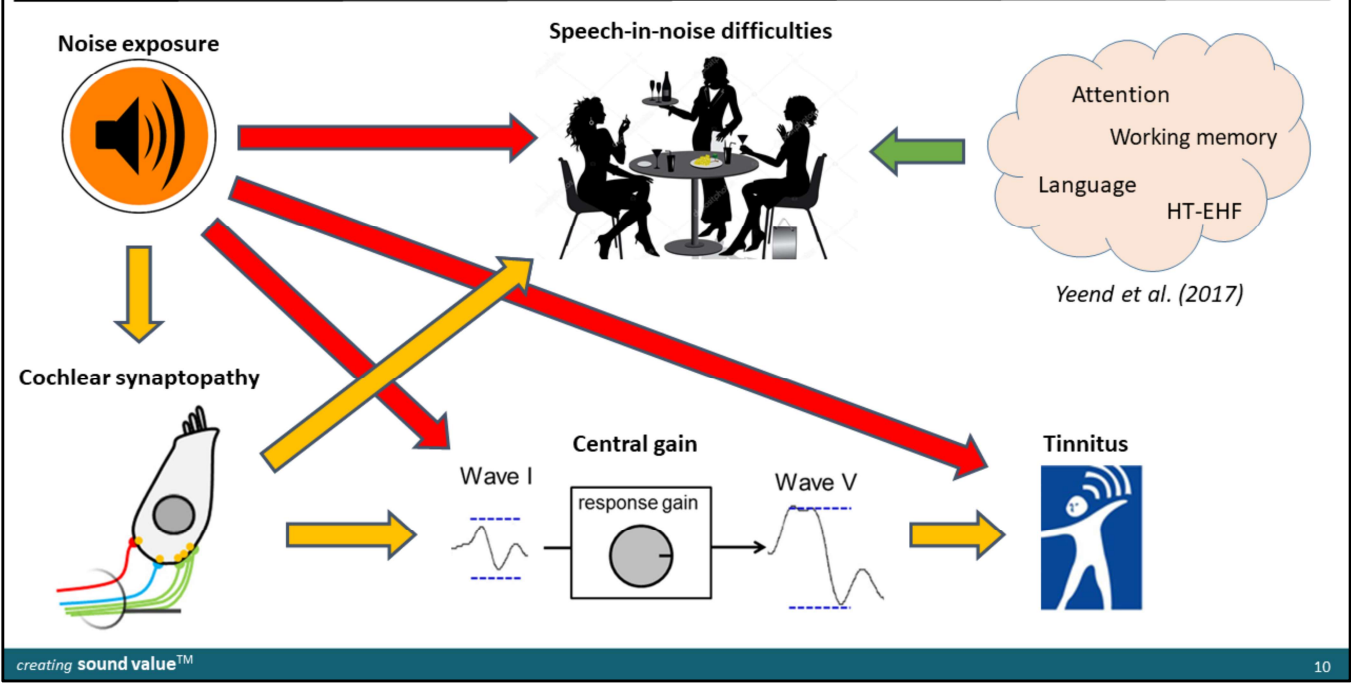
Is there a link between cochlear synaptopathy and SIN difficulties?



No direct association between speech-in-noise performance and cochlear synaptopathy

- However, our results showed no direct effect of  $A_1$  on speech-in-noise difficulties.

Summary



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- Taken together, what do these results indicate in the big picture?
- We observed (1) that noise exposure can cause cochlear synaptopathy, (2) that cochlear synaptopathy can lead to the activation of central gain mechanisms, and (3) that this neural reorganization may lead to tinnitus.
- However, we found no clear link between cochlear synaptopathy and speech-in-noise difficulties. One possible interpretation of this result is that noise exposure causes cochlear synaptopathy, that is later compensated by central gain mechanisms.
- Another possibility is that LNE in understanding speech in noise is not as important as other cognitive processes, which were found to play a relevant role in a previous study from the same research group, such as attention, working memory, and language.
- In addition, we also found that the effect of noise exposure on the human auditory system was not systematic or predictable, which means that not everybody with high levels of noise exposure had cochlear synaptopathy, central gain activated and tinnitus. It might also be the case that individuals show different levels of susceptibility to noise exposure.

## Take-home message

1. Noise exposure can cause cochlear synaptopathy, potentially leading to tinnitus.
2. There is no current standard test to diagnose or any efficient method to treat cochlear synaptopathy in humans.

Prevention is key

Valderrama JT, Beach EF, Yeend I, Sharma M, Van Dun B, Dillon H (2018). Effects of lifetime noise exposure on the middle-age human auditory brainstem response, tinnitus and speech-in-noise intelligibility. *Hearing Research, under review.*

Thank you very much for your attention



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- I would like to finalise by highlighting the two main “take-home messages” of this talk.
- Our results indicate that noise exposure can cause cochlear synaptopathy in humans.
- At the moment, there is no current standard test to diagnose this pathology, nor any efficient method to treat cochlear synaptopathy.
- In short, prevention is key. It is important to acquire healthy hearing habits and protect our ears from excessive noise exposure.
- If you are interested in knowing more details about this study, stay tuned to this publication that we expect to be accepted soon.
- Thank you very much for your attention.