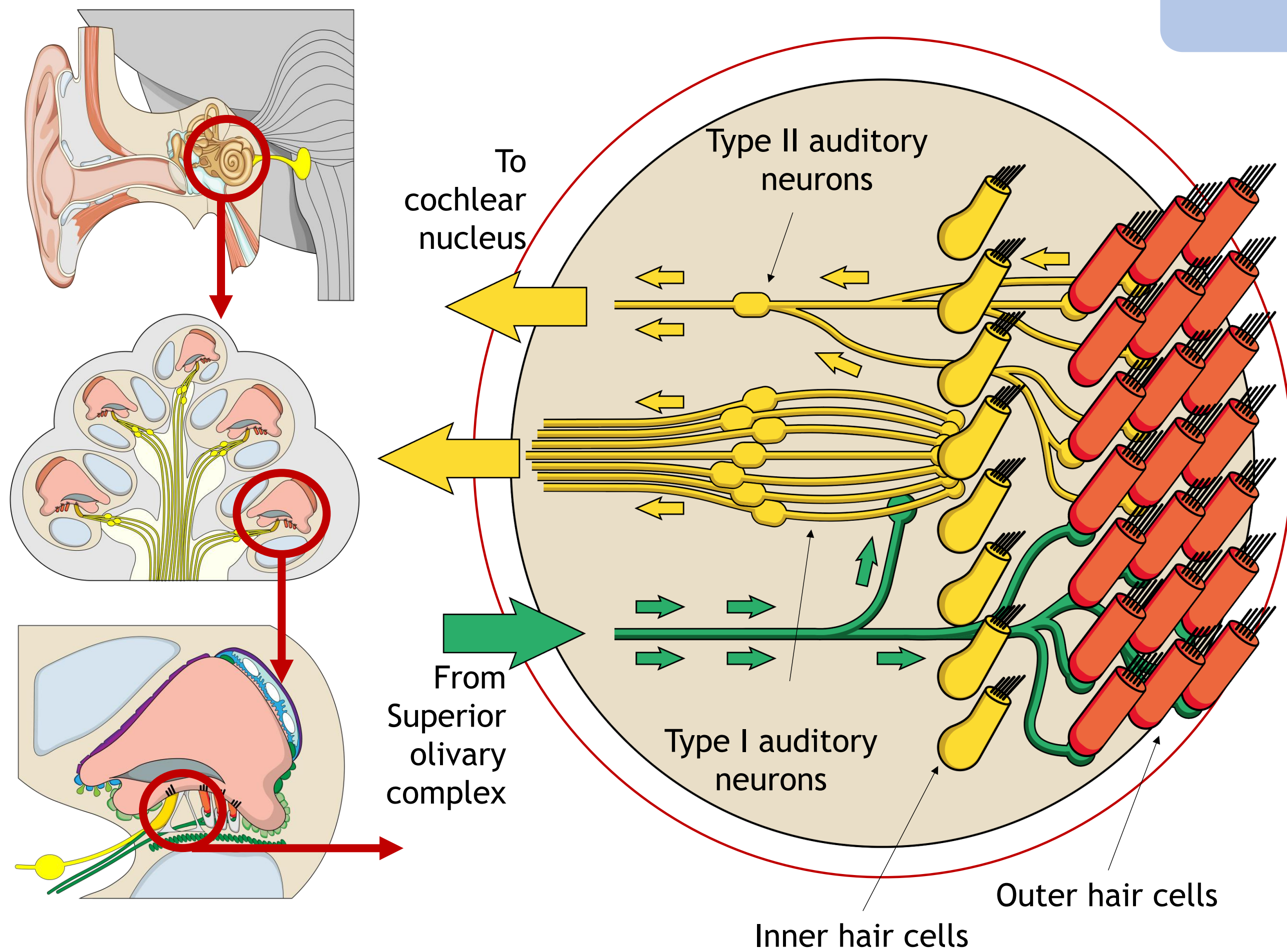
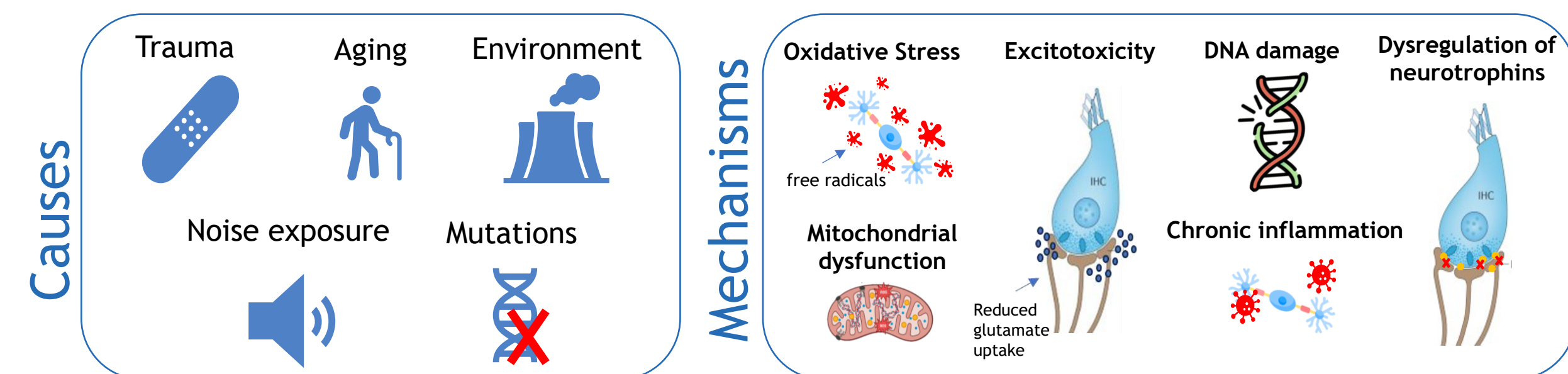


Neural Hearing Loss



Causes and pathophysiological mechanisms of Neural Hearing Loss²



Neural hearing loss describes hearing deficits resulting from loss or dysfunction of the auditory nerve, including the spiral ganglion neurons and/or their synaptic connections.¹

Neural health describes the structural and functional status of auditory neurons, including factors such as neural survival, synaptic integrity, and responsiveness to electrical or acoustic stimulation.¹

Auditory Neurons are important for...

Signal transmission from the cochlea to the brain

Sound discrimination of subtle differences in frequency and intensity allowing for complex listening

Loudness and Temporal information coding through firing patterns³



As a result, neural hearing loss can comprise everyday activities that require complex listening such as talking on the phone, listening to music, listening in background noise and group conversations.

Associated conditions

Presbycusis⁴

- 1 in 3 adults over the age of 60
- Mixed pathology

Post synaptic ANSD⁵

- Form of ANSD disrupted neural transmission beyond the IHC
- 5% of adults with mild to moderate hearing loss
- Paediatric and adult

Noise induced hearing loss⁴

- One of the most common occupational and environmental causes of acquired hearing loss

Tinnitus and Hyperacusis⁶

- Potentially due to central system gains

Diagnosis, assessment and management

Diagnosis and assessment

- Neural hearing loss remains underdiagnosed.
- PTA assessment is predominantly influenced by the function of the OHCs & IHCs, not neural health.
- Auditory neuron loss can proceed hair cell loss or it happen independently.
- Loss of more than 50% of auditory neurons is required before it impacts PTA measurements, concealing deficits in complex listening⁷.
- Tests like **speech-in-noise** or **auditory brainstem responses** (ABRs) are sensitive to these deficits but not all of these tests are always done routinely in clinical practice.

Take home message:

1. Normal audiogram $\neq$ Normal hearing
2. Speech testing (especially in noise) could help detect neural hearing loss

Treatments

There are no available treatments for neural hearing loss partly due to lack of diagnostic tools, partly because there are no effective interventions.

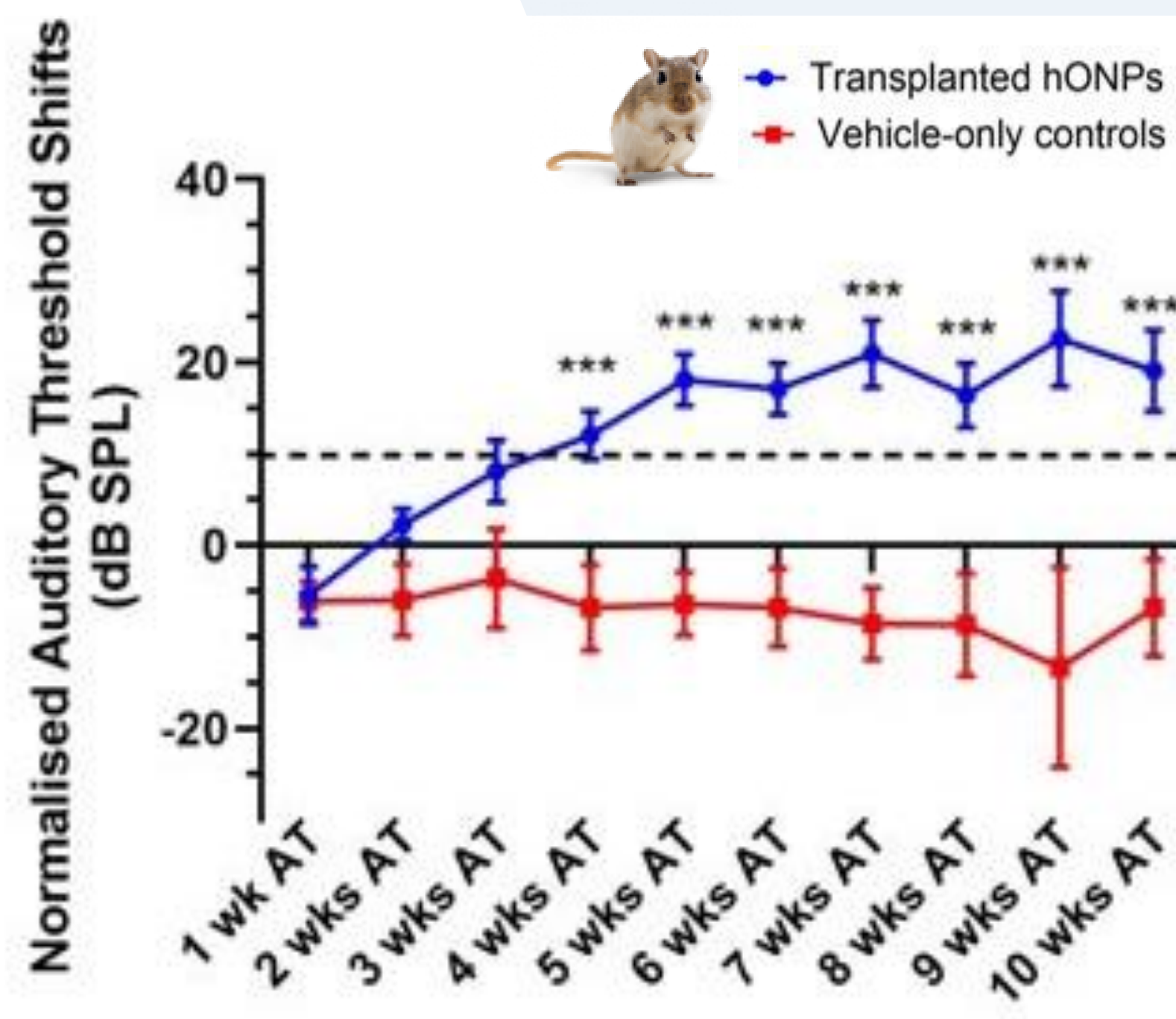
Hearing aids and cochlear implants (CIs) are not designed to address neural hearing loss but rather focus on overcoming sensory deficits and they rely on intact neural pathways.

Neural hearing loss drives variability in CI outcomes: larger populations of healthy auditory neurons $\rightarrow$ better speech outcomes⁸



Emerging Treatments

Cell therapies offer the potential to replace damaged auditory neurons and improve auditory signal transmission.



Rincell-1 is a cell therapy made from otic progenitors, cells that are one developmental stage before becoming matured auditory neurons⁹.

In animal and laboratory models Rincell-1 is:

- **Effective** - Can re-establish functional connections from the cochlea to the brainstem.
- **Safe** - Cells remain at the site of administration with no side effects observed.

In humans:

- Rincell-1 could help to **improve CI outcomes** by replenishing the population of auditory neurons.
- The therapy can be injected into the Internal Auditory Meatus via the Round Window using a new, safe, effective and minimally-invasive surgical technique¹⁰.
- Objective measures of neural health have been validated in existing and new cochlear implant users. These measures can be used to quantify the safety and efficacy of Rincell-1¹¹.

Discussion/ Next steps

Neural hearing loss represents a significant unmet clinical need and recognising and addressing neural pathology has the potential to transform hearing outcomes, particularly in presbycusis, and postsynaptic ANSD.

Next steps

1. **First in human clinical trial of Rincell-1:** A multi-centre, open-label randomised trial of Rincell-1 in conjunction to cochlear implantation in adults with presbycusis and post-synaptic ANSD. The trial will last for 13 months and will assess safety (frequency and severity of related adverse events), efficacy and feasibility (nerve survival and function, successful delivery) and maintenance and real-world benefit (treatment effect duration, speech perception and quality of life)¹².
1. **Reliable methods for detecting and monitoring neural hearing loss:** Measures and tests are being developed and validated with both existing and new cochlear implant users. These tools could be crucial for predicting CI outcomes, guiding expectations, and evaluating the efficacy of emerging therapeutic interventions.

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