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A Multi-Biomarker Battery for Stratifying Complex Sensorineural Hearing Loss and Predicting Listening Outcomes

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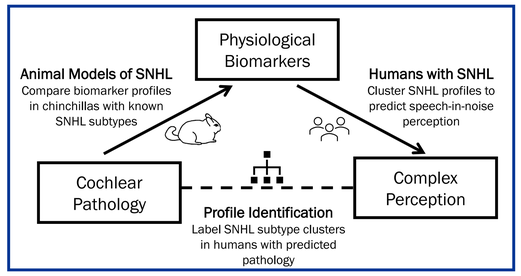
INTRODUCTION & FRAMEWORK

Sensorineural hearing loss (SNHL) is a complex pathology that potentially includes damage to the outer hair cells , the inner hair cells, the stria vascularis and the auditory nerve. Current diagnostic strategies for SNHL, however, do not allow clinicians to measure individual differences in the underlying anatomical variability. This important source of variability is also like to contribute to individual differences in perception or treatment outcomes.

In this study, we asked whether a battery of physiological biomarkers sensitive to OHC and non-OHC pathologies differentiates animals with variable exposure histories (and thus profiles of sensorineural injuries) and whether this battery can identify humans with poorer performance on speech-in-noise tasks.



A CROSS-SPECIES APPROACH

Biomarker Test Battery

Measure	Sensitive to…
Hearing Thresholds	OHC function, limited sensitivity to IHC and/or neural function [1, 2]
Swept DPOAE	OHC function [3]
Swept SFOAE	OHC Function, cochlear tuning [3]
Wideband Middle Ear Muscle Reflex (WB-MEMR)	Cochlear synaptopathy [4]
Envelope Following Response to RAM-stimuli (RAM-EFR)	Cochlear synaptopathy [5], IHC dysfunction
Click Auditory Brainstem Response (ABR)	EHF OHC function, Cochlear synaptopathy [2]

Chinchilla Models

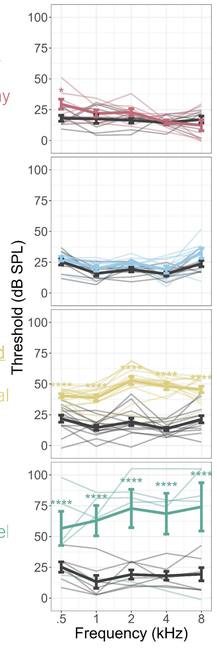
4 pre-clinical chinchilla models of sensorineural injury, two hidden hearing loss models and two overt SNHL

Noise-induced temporary threshold shift (TTS): Cochlear synaptopathy [4] (n = 8)

Carboplatin (CA) ~10% inner hair cell loss and stereocilia dysfunction [6] (n = 9)

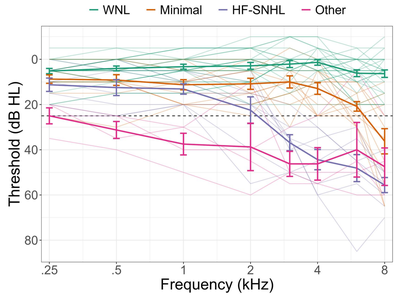
Noise-induced Permanent Threshold Shift (PTS) Complex sensorineural dysfunction [7] (n = 14)

Gentamicin (GE) Outer and inner hair cel loss [6] (n = 5)

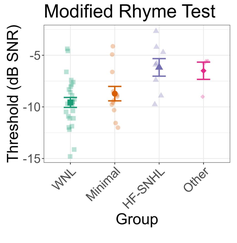


Human Participants

Adults with normal hearing or mild to moderate sensorineural hearing loss



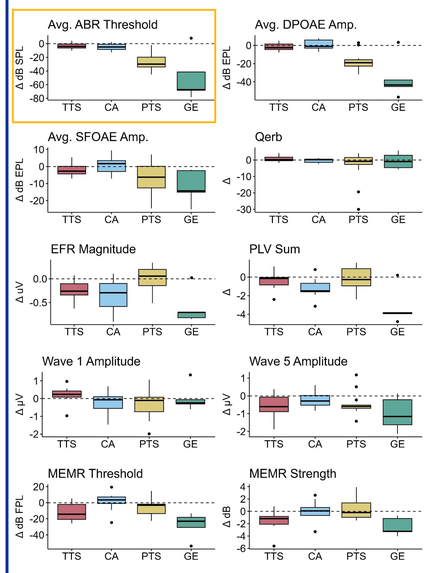
Participants were clustered based on four different **audiometric configurations**. Normal hearing (n =24), Minimal Hearing Loss (n=12), High-Frequency SNHL (n=8), and Other (n =4)



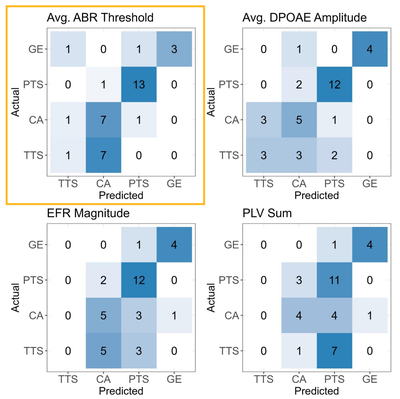
Participants completed the Modified Rhyme Test (MRT) in an inharmonic tone complex masker [8], revealing large individual differences across individuals with audiometrically-similar hearing sensitivity.

CLASSIFYING BY EXPOSURE HISTORY

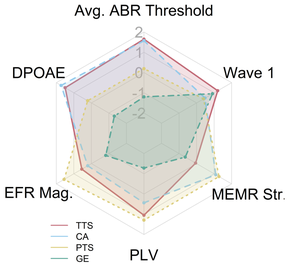
Individual metrics are poor predictors of exposure group and fail to differentiate models of CS from models of IHC dysfunction.

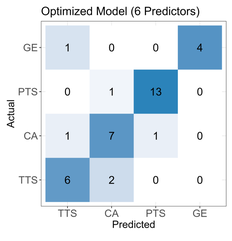


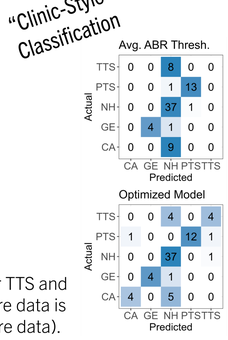
Using a multinomial regression model, the difference between pre- and post-exposure response were used to predict exposure group. Average ABR thresholds and DPOAE amplitudes give the highest accuracy at 67%. EFR metrics, magnitude and Phase Locking Value (PLV), have an accuracy of 58% and 53%, respectively.



Exposure group can be accurately identified in most animals using a multimetric approach that includes both measures of OHC and non-OHC function.



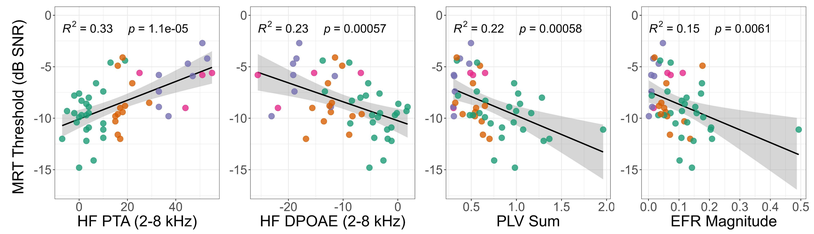




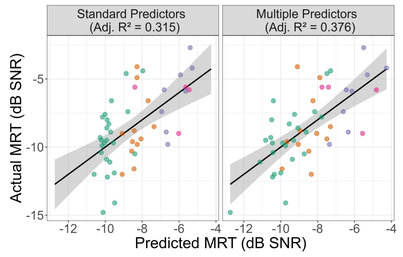
Overall accuracy increases to 83% with greatly improved performance for TTS and CA cases. Improved predictive strength holds when only the post-exposure data is used as is typical in clinical scenarios (NH = normal hearing, pre-exposure data).

PREDICTING LISTENING OUTCOMES

The audiogram, age, and many individual biomarkers are significantly correlated with performance, but none account for more than 33% of the variance in scores.



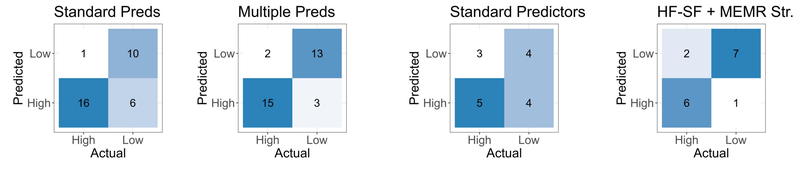
A multimetric approach that includes physiological biomarkers sensitive to OHC and non-OHC function improves prediction of speech-in-noise scores.



Standard Predictors = HF PTA, Age
Multiple Predictors = HF PTA, Age, SFOAEs, PLV Sum, Wave I Amp.

A combined model with **SFOAEs, PLV Sum, and Wave I amplitudes** explained 12% more variance than standard clinical predictors (HF-PTA, Age).

Physiological biomarkers improve sensitivity and specificity of speech-in-noise difficulty



Classification of "high" and "low" performing individuals (the top and bottom tertiles, respectively) is improved by the combined approach. In listeners with normal hearing, identifying low performing individuals is near chance levels. Accuracy, sensitivity, and specificity are greatly improved with HF SFOAE measures and MEMR strength.

CONCLUSIONS & FUTURE DIRECTIONS

The audiogram is insufficient for the detection of all inner ear pathologies and is inadequate to identify those most likely to struggle with speech-in-noise perception. A combination of measures sensitive to both OHC and non-OHC dysfunctions is needed to improve diagnostic specificity of SNHL. For heterogeneous cohorts of patients, developing and refining this multimetric approach is critical for differentiating pathophysiology profiles with high sensitivity and specificity.

Big Data

This profiling approach can be improved with a larger cohort of subjects. We are developing a cross-species infrastructure for auditory neuroscience data and associated data standards.

Cross-Species Insights

Insight from chinchilla models suggest that multimetric data will be critical to non-invasively dissect underlying cochlear targets for pharmaceutical interventions and other individualized treatments for hearing loss.

Future studies will apply insight from animals with known pathologies to humans with unknown anatomical profiles.

Other Studies

See results from our replication study in a second cohort of participants:

See results of cochlear histology from chinchillas with these pathologies:

REFERENCES

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