Differentiating Inner Hair Cell Dysfunction from Cochlear Synaptopathy Using Non-Invasive Measures of Temporal Envelope Coding in Chinchillas

Ivy Schweinzger, PhD [1] Andrew Sivaprakasam, BSE [2] Michael Heinz, PhD [1,2]

[1] Speech, Language, & Hearing Sciences, Purdue University
[2] Weldon School of Biomedical Engineering, Purdue University

HEINZ LABORATORY
Auditory Neurophysiology & Modeling

Introduction

The individual effects of damage to hair cell bodies, synapses, and stereocilia remain unclear.

Our group has previously demonstrated that selective damage to inner hair cells (IHCs) may alter auditory brainstem responses to high level stimuli and disrupt envelope coding[1]– a similar phenotype observed with cochlear synaptopathy[2].

Stimuli with sharply-modulated envelopes (e.g. square waves) are thought to bypass OHC effects and highlight synaptopathic damage[3], however, we must also consider the effects of potential inner hair cell body/stereocilia damage when making these observations. Changes in auditory functioning due to IHC damage leads to decreases in ANF spontaneous and driven rates[4,5] and could potentially lead to deficits in modulation coding.

The purpose of this study was to obtain envelope following responses to three amplitude-modulated stimuli to **observe differential effects of inner hair cell and synaptopathic damage** in a chinchilla model of carboplatin (IHC damage) and moderate noise exposure (synaptopathy-inducing noise exposure).

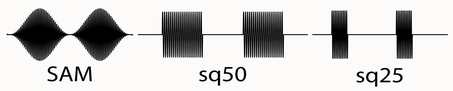
Methods

Chinchillas (N=8, 50% Female): Randomly assigned to equal sex-matched temporary threshold shift (TTS) and carboplatin-exposed (CA) experimental groups

Baseline data were taken from all animals and repeat measurements were collected 2 weeks following TTS or CA exposure.

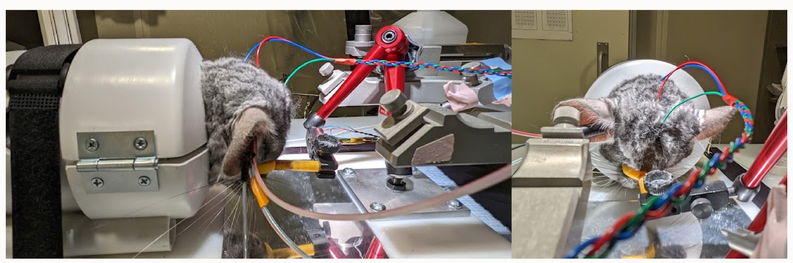
Data Collected:

- **Distortion Product Otoacoustic Emissions (dpOAEs)** with F2 from 500Hz - 10kHz
- **Wideband Middle-Ear Muscle Reflexes (MEMRs)** with broadband noise elicitor[6]
- **Envelope Following Responses (EFRs)** to square-modulated stimuli with 50% & 25% duty cycles (sq50 & sq25) and sinusoidally modulated (SAM) stimuli with 100 Hz modulations and a 4 kHz carrier.



Exposure:

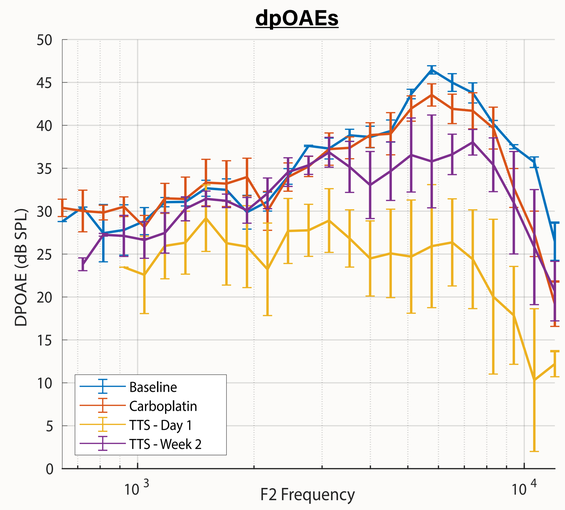
- **Carboplatin**, 38 mg/kg [4]
- **TTS**, Octave-band noise centered at 1 kHz, 100 dB SPL, 2 hrs



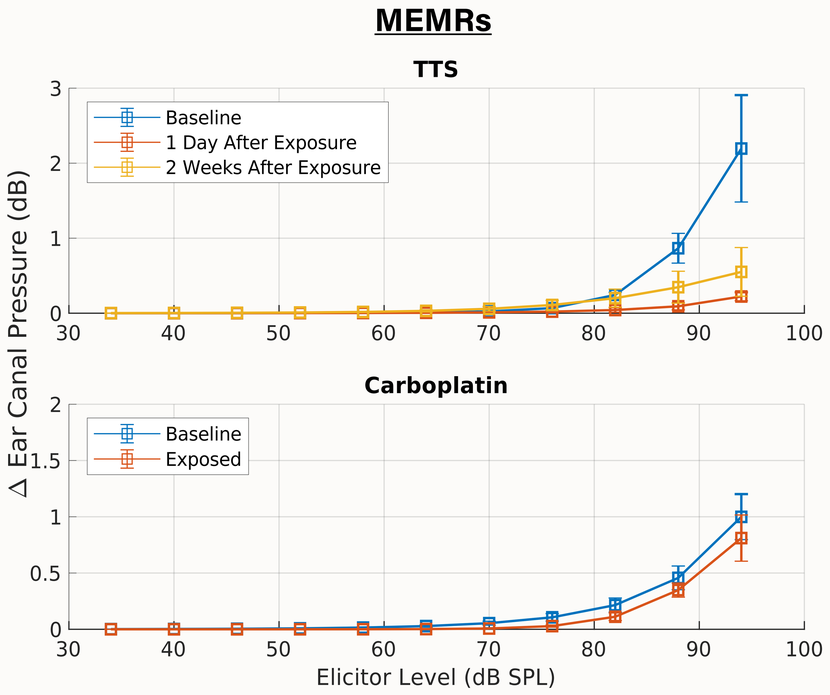
dpOAEs and MEMRs were collected while the animal was awake (above). EFRs were collected under anesthesia (induced with Ketamine and Xylazine).

Confirmation of Effect

In the TTS cohort, dpOAEs demonstrated an expected reduction in amplitude immediately following noise exposure, with a relative return to baseline within 2 weeks. As expected, carboplatin-related deficits induced by our protocol are IHC-specific and did not result in an appreciable change in dpOAEs. In the figure below, baseline data has been pooled from both cohorts. Error bars represent standard error of the mean.

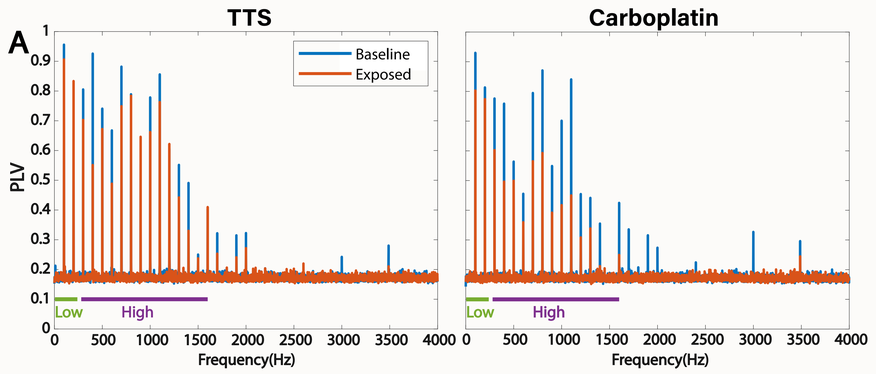


Consistent with our previous synaptopathy work[7], **MEMR amplitudes were markedly reduced in the TTS cohort. This amplitude reduction was not apparent in the CA group**, indicating carboplatin-mediated damage induced by this protocol may have spared low spontaneous rate cochlear synapses—thought to drive the MEMR pathway.

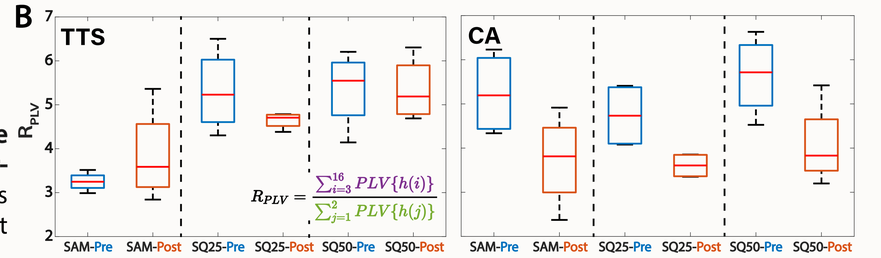


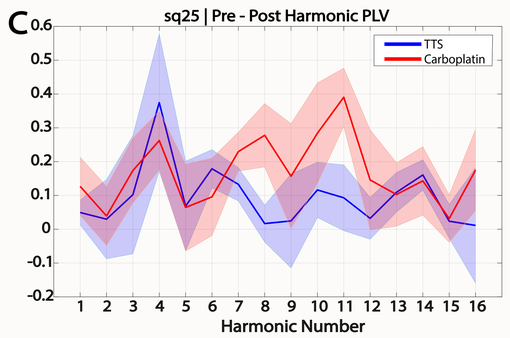
Electrophysiological Measures

EFRs were assessed using Phase-Locking Value (PLV)[8]. Panel **A** shows the mean PLV spectrum across all chinchillas in either cohort in response to the 25% duty cycle RAM stimulus (sq25). **Chinchillas in the carboplatin group demonstrated a stark deficit in modulation coding, particular in the higher harmonics, in response to all three stimuli after exposure. Chinchillas in the TTS group did not demonstrate as sharp of an effect.** This effect was quantified by computing the ratio of the sum of the PLV of the first two harmonics (Low) to the sum of the PLV of the 3rd through 16th harmonics (High) (Panel **B**).



Ratio (R_{PLV}) of High to Low Harmonics





From the distributions shown in **B**, our data indicated that the computed ratio was most consistently reduced in response to the sq25 stimulus. The reduction in PLV magnitude for each harmonic number is pictured in Panel **C**.

Conclusions

1. Our TTS and Carboplatin protocols, designed to induce Cochlear Synapse and IHC damage, respectively, resulted in MEMR and OAE measures that are in line with our expectations.

2. EFR responses to sharply-modulated tones highlight **deficits in modulation coding** that are **more appreciable with IHC damage**, and less so with synaptopathy.

3. Changes in driven rate and modulation coding are **likely due to a shallower IHC transduction non-linearity**. Neural firing to higher harmonics of RAM stimuli were degraded in the Carboplatin group compared to the TTS group, similar to results shown by Mepani et al., 2021[9], suggesting that selective **inner hair cell damage has a more significant impact on modulation coding deficits than synaptopathy**.

4. **The confounding effects of IHC damage in cases of suspected synaptopathy (TTS) should not be ruled out.** Deficits in phase-locking ability to modulated stimuli, measured using EFRs, appear to be a good measure of differentiating IHC damage and synapse-specific damage.

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References:

[1] Axe, D. R., Thesis, 2017 [2] Shaheen, L. A. et al. J. Assoc. Res. Otolaryngol., 2015 [3] Vasilkov, V. et al. Hear. Res., 2021 [4] Wang, J. et al. Hear. Res., 1997 [5] Lang, H. et al. J. Assoc. Res. Otolaryngol., 2010 [6] Feeney, M. P. , Keefe, D. H. Ear Hear, 2001 [7] Bharadwaj, H. M. et al. bioRxiv, 2021 [8] Zhu, L. et al. J. Acoust. Soc. Am, 2013 [9] Mepani, A. M. et al. J. Neurophysiol., 2021