An analysis of cochlear response harmonics: Contribution of neural excitation

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(Received 9 July 2015; revised 30 September 2015; accepted 12 October 2015; published online 11 November 2015)

In this report an analysis of cochlear response harmonics is developed to derive a mathematical function to estimate the gross mechanics involved in the *in vivo* transfer of acoustic sound into neural excitation (f_{Tr}). In a simulation it is shown that the harmonic distortion from a nonlinear system can be used to estimate the nonlinearity, supporting the next phase of the experiment: Applying the harmonic analysis to physiologic measurements to derive estimates of the unknown, *in vivo* f_{Tr} . From gerbil ears, estimates of f_{Tr} were derived from cochlear response measurements made with an electrode at the round window niche from 85 Hz tone bursts. Estimates of f_{Tr} before and after inducing auditory neuropathy—loss of auditory nerve responses with preserved hair cell responses from neurotoxic treatment with ouabain—showed that the neural excitation from low-frequency tones contributes to the magnitude of f_{Tr} but not the sigmoidal, saturating, nonlinear morphology.

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[BLM]

Pages: 2957–2963

I. INTRODUCTION

Sensory systems transfer environmental stimuli to excitation of neuronal membranes, and homeostatic mechanisms maintain stability of the sensory system. The transfer of the environmental signals in the ear is mediated by hair cells. Cochlear partition vibration opens and closes stereocilia ion channels, modulates the ongoing standing current, and with it hair cell polarization sets off a complex cascade of events resulting in neurotransmitter release and auditory nerve excitation. Mechanics associated with this sound transfer are mostly nonlinear (f_{Tr}). Otoacoustic emission and cochlear response¹ measurements have been used to derive mathematical estimates of f_{Tr} and, when expressed as the assumed basilar membrane displacement, were shown to have similar attributes of more direct measurements of cochlear mechanics: a sigmoidal, saturating, nonlinearity (cf. Cheatham and Dallos, 1997 and Choi *et al.*, 2004, as examples).

Derived estimates of f_{Tr} from ears with hearing loss could potentially be used to differentially diagnose sensory from neural hearing loss and guide treatment approaches. For example, derived estimates of f_{Tr} were shown to differentiate between animal models of diseased states following manipulation to outer hair cell bodies from salicylate treatment, outer hair cell stereocilia during² temporary threshold shift from acoustic over exposure, ion homeostasis from furosemide treatment, and potassium channels that are widely distributed throughout the cochlea from pharmacological treatment (Patuzzi and Moleirinho, 1998; Bian and Chertoff, 1998, 2001; Sirjani *et al.*, 2004). Derived estimates of f_{Tr} have also been shown to differentiate between moderate to large degrees of endolymphatic hydrops in both animals and humans (Sirjani *et al.*, 2004; Brown and Gibson, 2011),

provide insight into the diseased mechanics of hearing in ears with endolymphatic hydrops from sustained displacement of the cochlear partition (Salt *et al.*, 2009), identify the spatial origin of cochlear responses in ears with wide ranges of damage from acoustic overexposure (Chertoff *et al.*, 2003), and vary with endocochlear potential changes from hypoxia (Brown *et al.*, 2009). Together, these findings suggest that derived estimates of f_{Tr} have translational promise to differentially diagnose sensory from neural hearing loss in human ears that are otherwise assumed to process sound with similar pathologic mechanics and are thus treated with similar hearing aid signal processing strategies.

Common approaches to deriving estimates of f_{Tr} use slow biasing of cochlear mechanics with a low-frequency tone presented alone or in combination with moderate- to high-frequency tones. Interpreting the results of amplitude modulation requires assumptions on how moderate to intense low-frequency sounds produce modulatory effects throughout the cochlea (e.g., Nieder and Nieder, 1971; Bian *et al.*, 2002; Abel *et al.*, 2009; Brown *et al.*, 2009; Brown and Gibson, 2011) and new information shows that the strength of modulation is not constant everywhere along the length of the basilar membrane (Lichtenhan, 2012; Lichtenhan and Salt, 2013). If basilar membrane displacement to a low frequency tone is not everywhere constant and in phase along the cochlear spiral, electrical responses of differing polarity from many cells will sum and consequently smooth the amplitude of the cochlear response. Moreover, slow biasing of cochlear mechanics with a low-frequency tone has largely ignored the contribution of neural excitation that is predominately phase locked to low-frequency tones (Henry, 1995; He *et al.*, 2012; Lichtenhan *et al.*, 2013; Lichtenhan *et al.*, 2014; Stankovic and Guinan, 1999). That is to say, low frequency tones evoke both hair cell and neural responses. Estimates of f_{Tr} from hair cells alone without neural

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contributions would be useful to differentially diagnose sensory from neural hearing loss. In the present study we (i) propose a theory and simulation that uses harmonic output of a nonlinear system to derive mathematical estimate of the nonlinearity, (ii) demonstrate how to use cochlear response harmonics from moderately intense low-frequency tones to derive a polynomial equation estimate of f_{Tr} , and (iii) quantify the contribution of neural excitation to derived estimates of f_{Tr} .

II. THEORY

The harmonic output of a system in response to a single frequency input can be used to estimate a function describing the nonlinearity that is the origin of the generated harmonics (Atherton, 1982). The output of the system $y(\theta)$ can be written as a Fourier series

$$y(\theta) = \sum_{n=0}^{\infty} a_n \cos(n\theta) + b_n \sin(n\theta), \quad (1)$$

where

$$a_n = \frac{\varepsilon_n}{2\pi} \int_{-\pi}^{\pi} y(\theta) \cos(n\theta) d\theta, \quad (2)$$

ε_n is the Neumann factor defined as 2 for $n = 0$ and 1 for $n \geq 1$, and

$$b_n = \frac{1}{\pi} \int_{-\pi}^{\pi} y(\theta) \sin(n\theta) d\theta. \quad (3)$$

For now we assume that the nonlinearity, N , is a single-valued nonlinear function. If the input to the system is $A \cos(\theta)$, and substituting θ in terms of x , such that $\theta = \cos^{-1}(x/A)$ into Eq. (2), then

$$a_n = \frac{1}{\pi} \int_{-A}^A N(x) \cos \left\{ n \cos^{-1} \left(\frac{x}{A} \right) \right\} \{A^2 - x^2\}^{-(1/2)} dx, \\ b_n = 0. \quad (4)$$

Recognizing that $\cos \{n \cos^{-1}(x/A)\}$ is the Chebyshev polynomial $T_n(x/A)$, and $\{\pi(A^2 - x^2)^{1/2}\}^{-1}$ is the amplitude probability density function for a sinusoid $r(x)$, we see that

$$a_n = \int_{-A}^A N(x) T_n \left(\frac{x}{A} \right) r(x) dx. \quad (5)$$

Now, our goal is to find $N(x)$. If we express $N(x)$ as a sum of Chebyshev polynomials

$$N(x) = \sum_{j=0}^{\infty} \alpha_j T_j \left(\frac{x}{A} \right), \quad (6)$$

it can be shown with the orthogonal relation $\int_{-A}^A T_j(x/a) T_n(x/a) r(x) dx = \delta_{nj}/\varepsilon_n$, where δ_{nj} is equal to zero for $n \neq j$ and 1 for $n = j$ and substituting Eq. (6) into Eq. (5) $a_n = \alpha_n$, results in

$$N(x) = \sum_{n=0}^{\infty} a_n T_n \left(\frac{x}{A} \right). \quad (7)$$

This demonstrates that a function describing the nonlinearity that creates harmonic distortion can be written as a sum of Chebyshev polynomials, each weighted by the Fourier series coefficient, a_n . That is to say, f_{Tr} could be obtained from the Fourier analysis of the cochlear response, the coefficients used to weight a polynomial equation, and used to obtain indices (e.g., operating point, dynamic range) which has been done in previous work (e.g., Chertoff *et al.*, 1996; Patuzzi and Moleirinho, 1998; Sirjani *et al.*, 2004). The theory we present advances on previous work.

III. SIMULATION

To demonstrate the application of the theory, we developed the following simulation. A signal $x = A \cos(\omega t)$, where $\omega = 2\pi f t$ and $f = 2$, served as the input signal to the odd-order nonlinear function,

$$y(t) = \frac{c}{(1 + e^{-dx})} - \frac{c}{2}, \quad (8)$$

where $c = 2$ and $d = 5$. The input signal, transfer function, and response are illustrated in Figs. 1(A)–1(C). The output signal, $y(t)$ was periodic with same period as the input signal but the relative extrema were flattened compared to the input signal. A fast Fourier transform (FFT) of the response [Fig. 1(D)], shows that the output signal contained the frequency of the input signal, f_0 , and odd harmonics $= (2n + 1)f_0$. The amplitude of the fundamental frequency and harmonics were used to scale the Chebyshev polynomials in Eq. (7). Ten harmonics were used (i.e., $n = 10$), but because of the odd symmetry of the function, only five odd-order terms were actually necessary. The results showed that the estimated transfer function $N(x)$ was identical to the original transfer function, and is illustrated in Fig. 1(E) where $N[x(t)]$ and $y[x(t)]$ are plotted versus $x(t)$. Moreover, the estimated transfer function, $N(x)$ accurately estimated the output waveform, Fig. 1(F).

IV. METHODS

A. Overview

Measurements were made from the right ear of female Mongolian gerbils weighing between 45 and 70 g. Ouabain, which abolishes auditory nerve responses while maintaining hair cell responses (e.g., Schmiedt *et al.*, 2002; Lang *et al.*, 2005; Peppi *et al.*, 2012; Yuan *et al.*, 2014) was used to quantify the extent to which neural excitation contributes to f_{Tr} . All experiments were acute in that on a given day a pharmaceutical treatment was applied, an experiment performed, and the animal was sacrificed. One group of gerbils was treated with 1 mM ouabain in artificial perilymph (AP) applied to the round window niche, and the second group of received AP only. Measurements for this report were collected for approximately 15 min, then data for other studies were collected for 30–45 min. Next, 1–2 μ L of either ouabain

FIG. 1. A simulation to demonstrate that the new harmonic analysis can be used to estimate the nonlinearity that produced the output. The single-frequency input (A) was used to probe the nonlinearity [(B); Eq. (8)] and obtain an output (C) and (D). Using the output spectrum (D) and the harmonic analysis described in Sec. II, we estimated the nonlinearity that produced the harmonics (E). Simulated refers to the nonlinear function described by Eq. (8). Probing the estimated nonlinearity with a single-frequency input yields an output that is strikingly similar to the original (F).

in AP or AP only was applied to the gerbil round window niche for 30 min, then subsequently wicked from the niche. After an additional 30 min, measurements were repeated. Ouabain was dissolved in AP. The composition of gerbil AP (mM) was NaCl (120), KCl (3.5), CaCl_2 (1.5), glucose (5.5), HEPES (20), and the pH was adjusted to 7.5 with NaOH (Chertoff *et al.*, 2014). Procedures were approved by the Animal Care and Use Committee at the University of Kansas Medical Center.

B. Surgical procedures

Animals were sedated with 64 mg/kg pentobarbital, and one-third this dose administered every hour. The right hind thigh was shaved and a pulse-ox meter was placed on the thigh to monitor heart rate and blood oxygen. The right pinna was removed and the skin and muscle separated and retracted until a clear view of the bulla was obtained. Next, the animal was wrapped in a heating pad and placed in a head holder. The bulla was opened with a sharp pick and enlarged with forceps until the round-window niche was visualized. A ball electrode, attached to a micro manipulator, was lowered into the round-window niche. A second electrode was placed in the thigh and served as ground.

C. Acoustic stimuli

Cochlear responses were evoked with 85 Hz tone-bursts with 15 ms rise/fall times and a 70 ms plateau, presented 50 times at 5 per s. Signals were created in BioSig from Tucker-Davis Technology (TDT), uploaded to an RZ6 (TDT) module, attenuated (PA4, TDT), and amplified (SA1 Power Amplifier, TDT). The signals were delivered to a 12 cm diameter speaker placed outside the acoustic chamber that was coupled to a tube passing through a hole in the wall of the acoustic chamber and routed sound to the bony ear canal. The tube served two purposes: (i) the length was chosen to emphasize 85 Hz to achieve desired sound pressure

levels, and (ii) the length physically separated the speaker electromagnetics from the recording electrodes. Cochlear responses to 85 Hz tones were monitored while adjusting the angles of the tube and skull to maximize response amplitude. Compound action potentials (CAPs) were evoked with 1, 2, 4, 8, 16, and 24 kHz tone bursts with 1 ms rise/fall times and a 8 ms plateau, presented approximately 50–500 times (fewer presentations for higher signal levels) at 21.1 per s at 100 to 5 dB sound pressure level (SPL) in descending order, and delivered through a headphone (MF1, TDT) positioned approximately 5 mm from the open end of the tube. Acoustic stimuli were calibrated with a [1/4] in. Bruel and Kjaer microphone (model 4938) and amplifier (Bruel and Kjaer, Nexus conditioning amplifier) placed in front of the open end of the tube.

D. Data acquisition

Cochlear responses were measured (BioSig controlling a TDT RZ6 module, 175 ms response windows sampled at 200 kHz), amplified (Stanford, 50 $\times$), filtered (0.03 to 30 000 Hz), further amplified (100 $\times$) and low-pass filtered (Stewart, 3 kHz). Sampling resolution was chosen such that the spectral bins were equivalent to the frequencies of cochlear response harmonics.

E. Statistical analysis

A linear mixed model analysis quantified the influence of ouabain on gerbil CAP level series. For each probe frequency, the following model was used:

$$\begin{aligned} \ln(y) = & b_0 + b_1x + b_2x^2 + b_3x^3 + b_4(\text{Group by } x) \\ & + b_4(\text{Group by } x^2) + b_5(\text{Group by } x^3) + \varepsilon, \end{aligned}$$

where $\ln(y)$ is the natural logarithm of the CAP amplitude, b are regression coefficients to be estimated, x is signal level in dB SPL, and Group is 0 for the AP-treated animals, 1 for

ouabain-treated animals, and represents the interaction between group and signal level. The error of the model is indicated by ε . The natural logarithm was used to reduce heteroscedasticity in the CAP amplitude-level growth functions. This model was fit using maximum likelihood estimation, and sequential backward elimination was used to eliminate non-significant terms, i.e., $p \geq 0.05$. A significant effect was defined for $p \leq 0.05$.

V. RESULTS

A. Empirical estimation of the *in vivo* f_{Tr}

Cochlear responses to 80 dB SPL 85 Hz tone bursts were similar across gerbils ($n = 16$), had square-wave-like morphology, and small multi-phasic deflections at the maxima and minima [Fig. 2(A)]. Amplitudes in the average spectra were largest at the fundamental and third harmonics [Fig. 2(B)]. The derived f_{Tr} using 10 terms in Eq. (7) was a sigmoidal function that was not entirely odd, as the minimum peak was larger than the maximum peak and approached $-250 \mu\text{V}$ whereas the maximum was approximately $200 \mu\text{V}$ [Fig. 2(C)].

Derived f_{Tr} from average cochlear responses from 70 to 50 dB SPL [Fig. 3(A)] was sigmoidal at the highest levels and linear at lower levels [Fig. 3(B)]. The nonlinear morphology of the derived f_{Tr} did not originate from harmonic distortion in the acoustic stimulus, in that the harmonic analysis [Eq. (7)] of measurements from the acoustic assembly in the ear canal yielded a linear transfer function [Fig. 2(C) inset]. The estimated cochlear response calculated from the derived f_{Tr} was similar to the empirically obtained cochlear responses from 85 Hz tone bursts at 80 dB SPL [Fig. 2(D)] down to 50 dB SPL [Fig. 3(C)]. These results indicate that the derived f_{Tr} from the harmonic analysis could accurately

describe the transfer of acoustical stimulation into the cochlear response outputs.

B. Neural contribution

CAP amplitudes were reduced following treatment with ouabain as compared to those who received AP only, particularly to high-frequency tone bursts (i.e., 24, 16, and 8 kHz) and less so to low-frequency tone bursts (i.e., 4, 2, and 1 kHz) (Fig. 4).

The linear mixed model analysis showed that CAP differences were significant between the ouabain- and AP-treated animals, with the greatest effect for the high frequencies. Compared to AP application alone, ouabain treatment to the gerbil round window niche increased the variability of cochlear response to 80 dB SPL 85 Hz tones [cf. Figs. 5(A) and 5(B)] and altered the extremes of the mean f_{Tr} [Fig. 5(C)]. Amplitudes of the fundamental and third harmonic were not statistically different before and after ouabain treatments to gerbil (fundamental, $t = 2.04$, $p = 0.06$; third harmonic, $t = 1.61$, $p = 0.13$). However, the achieved statistical power was < 0.2 , limiting the interpretation of the statistical analysis. Erroring on the side of caution, we conclude that ouabain altered the amplitude of the fundamental of the cochlear response but not the third harmonic. These results indicate that neural excitation in the basal half of gerbil cochleae contributed to the magnitude, but not the nonlinearity of the derived f_{Tr} , and thus the f_{Tr} can describe much of the macro mechanics involved in the transfer of acoustic sound into neural excitation.

VI. DISCUSSION

A. Harmonic analysis applied to cochlear responses

The theoretical considerations and simulation results of this study showed that harmonic distortions can be used to

FIG. 2. (A) Individual (dotted lines) and average (solid line) cochlear responses from 80 dB SPL 85 Hz tone bursts (signal level indicated in the far right of the panel). (B) The frequency domain spectrum of the average cochlear response in (A) shows predominantly odd harmonics. (C) The new harmonic analysis [Eq. (7)] applied to the cochlear response and the ear canal acoustics, respectively, derive an estimate of f_{Tr} and demonstrate that the origin on harmonic distortion is not from the acoustic stimulus (inset). (D) Estimated cochlear response (circles) closely approximate the original cochlear response from (A) (solid line).

FIG. 3. (A) Gerbil cochlear responses measured with a round window electrode from 70, 60, and 50 dB SPL 85 Hz tone bursts. Cochlear responses from individual ears are dotted lines and the averages are solid lines. Signal levels are indicated to the far right in (A) and (C). (B) Derived f_{Tr} from the average cochlear responses in (A). As signal level decreased, the derived f_{Tr} was less nonlinear. (C) Output from the derived f_{Tr} (circles) closely approximates empirical cochlear responses (solid line), validating that the new analysis of cochlear response harmonic distortion adequately describes the *in vivo* f_{Tr} .

derive mathematical estimates of a nonlinear system that gave rise to the distortion. The new harmonic analysis was applied to empirical cochlear response harmonics from moderate to high stimulus levels recorded with an electrode near the round window membrane and yielded a sigmoidal, saturating, nonlinear f_{Tr} . As the stimulus level decreased, the derived estimates of f_{Tr} linearized and the slope steepened at 0 Pa (or the operating point). Ouabain applied to the round window markedly reduced neural excitation in the basal half of the cochlear spiral, consistent with the idea that solutions applied to the cochlear base are limited to treating only the basal half of the cochlear spiral (Salt and Ma, 2001; Chen *et al.*, 2005; Le Prell *et al.*, 2014), increasing the magnitude but not the general sigmoidal saturating morphology of derived f_{Tr} estimates.

FIG. 4. Gerbil compound action potential (CAP) measurements after application of artificial perilymph (open circles) or treatment with ouabain ($\times$'s). Error bars are standard error of the mean estimates. CAPs to high frequency tone bursts at all signal level were abolished by ouabain treatment. CAPs to low-frequency tone bursts were reduced at high levels but were largely unaffected at low levels, consistent with (i) high level responses originating from excitation of neurons in the cochlear base, likely the low-frequency tails of high-characteristic frequency fibers, and (ii) that round-window applied solutions do not reach the apical half of the cochlear spiral.

B. On the origins of the cochlear response used to derive estimates of f_{Tr}

Direct measurements of single-hair-cell mechanoelectric transduction and single-auditory-nerve-fiber excitation as a function of assumed displacement have sigmoidal, saturating, nonlinear functions (e.g., Russell and Kossel, 1991; Cai and Geisler, 1996). Similar to previous work using distortion product otoacoustic emissions and far-field evoked potentials, our derived estimates of f_{Tr} had less asymmetry than direct single-cell measurements (cf. Russell and Kossel, 1991; Chertoff *et al.*, 1996; Bian *et al.*, 2002). Considering the origins of gross measurements can help interpret our finding of limited asymmetry. The electro-anatomy of the cochlear spiral generates a complex electric field, and a source does not simply propagate longitudinally toward a round window electrode (Chertoff *et al.*, 2012). Responses from multiple origins with various phases, including those from outer hair cells, inner hair cells, the lateral wall, synapses, and auditory nerve fibers are summed vectorially in gross electrophysiologic measurements. Vector summation of responses can smooth measurements and may have influenced our finding of limited asymmetry after neural abolition. Lowering the frequency of the sound stimulus minimizes, but does not eliminate, the influence problematic vector summation because responses are supposedly more in phase with one another. But, the effect of moderate- to high-level, low-frequency sounds is not constant everywhere along the cochlear spiral (Lichtenhan, 2012; Lichtenhan and

FIG. 5. Gerbil cochlear responses to 80 dB SPL 85 Hz tone bursts measured with a round window electrode after treatment with ouabain (A) or artificial perilymph (B) applied to the round window. Dotted lines are measurements from individual ears and solid lines are averages. As compared to application of artificial perilymph (thin line), ouabain abolition of auditory nerve fiber responses in the cochlear base increased the extrema of the f_{Tr} derived from average cochlear responses, (thin line) (C).

Salt, 2013) meaning that vector summation can influence round window measurements even at very low frequencies. Thus, out-of-phase responses may have contributed to cochlear responses despite our use of 85 Hz which is certainly quite low in frequency. In the future, when deriving estimates of f_{Tr} the contribution of neural excitation could be further minimized by using measurements from inside the scala media where hair cell responses are large and

effectively isolated from the contribution of neural excitation (Lichtenhan *et al.*, 2014, Figs. 7 and 8c,d) or the use of infrasound (Lichtenhan and Salt, 2013).

C. Technical considerations

In the theory of using the amplitude of cochlear response harmonics to derive estimates f_{Tr} , the amplitude of the Fourier coefficients weights the Chebyshev polynomials. An important consideration is that the stimulus has cosine phase. That is, $\cos\{n \cos^{-1}(x/A)\}$ in Eq. (4) is the Chebyshev polynomial $T_n(x/A)$. This would not be the case if the argument of cosine was the arcsine function and the theory would not proceed. This presented a problem in that the data used in this report were from ongoing studies. Since our tone burst stimuli started at zero phase, we had to remove two cycles of the cochlear response at a cosine phase time point in order to use the theory. The real and imaginary terms for the fundamental of the fast Fourier transform of this segment were evaluated and the position in the waveform where the segment was extracted was modified until the imaginary component was small and the real part of the third harmonic was negative. The negative coefficient of the third harmonic was important, as it governed the saturation of f_{Tr} and thus the excellent estimation of the response cochlear responses. If the sign was positive, the f_{Tr} was expansive and the prediction of the physiologic response was poor. Constraining our use of cosine cochlear responses minimized Lissajous in our measures, as hysteresis is present in cochlear mechanics (e.g., LePage, 1992) but its influence on derived estimates of f_{Tr} is not yet fully understood. Similarly, the influence of cochlear amplification on derived estimates f_{Tr} is not yet understood.

VII. CONCLUSIONS

Measurements of cochlear response harmonics with an electrode in the round window niche from moderate to intense low-frequency tone-bursts were used in a new analysis technique to derive gross estimates of transfer of acoustic sound into neural excitation in the cochlea (f_{Tr}). f_{Tr} was found to be odd-symmetric, sigmoidal, and saturating. Neural excitation in the basal half of the cochlear spiral contributed to the, fundamental component, or magnitude of f_{Tr} , but not the harmonic distortion. These results show that, regardless of analysis technique, classic and future efforts to derive estimates of f_{Tr} from gross electrical measurements for basic and differential diagnostic purposes ought not to neglect the contribution of neural excitation.

ACKNOWLEDGMENTS

We thank Professor John J. Guinan, Jr. and Professor Alec N. Salt for productively criticizing earlier versions of this report. J.T.L. was supported by R03 DC012844 from the National Institutes of Health, National Institute on Deafness and Other Communication Disorders.

¹A few examples of cochlear response origins are the cochlear microphonic from inner and outer hair cells, summing potential, changes to the lateral wall potential from slow or sustained current through hair cells, excitatory

- postsynaptic potentials, compound action potentials from onset or phase locked sound pressure variations, and the coalescence with spontaneous excitation of single-auditory-nerve-fibers.
- ²Not to be confused with cochlear synaptopathy that occurs after, not during, temporary hearing loss from acoustic overexposure (e.g., Kujawa and Liberman, 2009).
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