Temporary hearing loss influences post-stimulus time histogram and single neuron action potential estimates from human compound action potentials

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An analytic compound action potential (CAP) obtained by convolving functional representations of the post-stimulus time histogram summed across auditory nerve neurons [$P(t)$] and a single neuron action potential [$U(t)$] was fit to human CAPs. The analytic CAP fit to pre- and postnoise-induced temporary hearing threshold shift (TTS) estimated *in vivo* $P(t)$ and $U(t)$ and the number of neurons contributing to the CAPs (N). The width of $P(t)$ decreased with increasing signal level and was wider at the lowest signal level following noise exposure. $P(t)$ latency decreased with increasing signal level and was shorter at all signal levels following noise exposure. The damping and oscillatory frequency of $U(t)$ increased with signal level. For subjects with large amounts of TTS, $U(t)$ had greater damping than before noise exposure particularly at low signal levels. Additionally, $U(t)$ oscillation was lower in frequency at all click intensities following noise exposure. N increased with signal level and was smaller after noise exposure at the lowest signal level. Collectively these findings indicate that neurons contributing to the CAP during TTS are fewer in number, shorter in latency, and poorer in synchrony than before noise exposure. Moreover, estimates of single neuron action potentials may decay more rapidly and have a lower oscillatory frequency during TTS. © 2008 Acoustical Society of America. [DOI: 10.1121/1.2885748]

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I. INTRODUCTION

Goldstein and Kiang (1958) proposed a theory that the compound action potential (CAP) is a summation of multiple single neuron action potentials. The summation is described mathematically by the convolution of an action potential from a single auditory nerve neuron with a probability density function representing a neuron's discharge timing and then scaling the convolution by the number of neurons contributing to the CAP. Various investigations of the CAP convolution model since 1958 up to present times have been reviewed elsewhere (Chertoff, 2004) and are not repeated here.

Chertoff (2004) revisited the CAP model by convolving a gamma distribution function representing a summed post-stimulus time histogram [$P(t)$] from an auditory nerve neuron with a decaying sine wave representing a single-neuron action potential [$U(t)$] to obtain an analytic CAP. That is,

$$CAP(t) = N \int_{-\infty}^t P(\tau) U(t - \tau) d\tau, \quad (1)$$

where

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$$P(t) = \left(\frac{t - \alpha}{\beta} \right)^{\gamma-1} e^{-((t-\alpha)/\beta)} \quad (2)$$

and

$$U(t) = e^{-Kt} \sin(\omega t). \quad (3)$$

According to this model t represents time in milliseconds, N is the number of neuronal units contributing to the CAP, and τ is a dummy variable. The width and location of the maximum of $P(t)$ is governed by the value of β , and γ is held constant at a value of 2. $U(t)$ decays by the power of K and $\omega = 2\pi F$, where F is frequency in hertz. The solution to Eq. (1) is provided in the Appendix and will be referred to as the “analytic CAP” throughout this manuscript. By fitting this analytic CAP to tone-burst evoked CAPs recorded from the round window of normal hearing gerbils, Chertoff (2004) provided estimates of the *in vivo* $P(t)$ and $U(t)$ and found that the number of neurons contributing to the CAP (N) and the $P(t)$ width (β) increased with signal level while the latency (α) decreased. These findings not surprisingly suggested that with high signal levels, neurons in the basal cochlear region contributed to the CAP for all tone-burst frequencies and at low signal levels CAP neural generators were located at their corresponding characteristic cochlear frequency place. Chertoff (2004) also found that the frequency of $U(t)$ oscillation (F) essentially increased with stimulus frequency and that $U(t)$ damping (K) was greater for 8 kHz tone bursts compared to the other tone-burst stimulus frequencies. This implied that hair cell and/or neu-

ral generators may not everywhere be homogeneous in physiology throughout the cochlear partition.

With the aim of translating the analytic CAP into a clinically useful tool for describing the physiology of the auditory nerve in the presence of hearing loss, we demonstrated that the analytic CAP could be fit to CAPs from gerbils with permanent hearing loss and that noise-induced cochlear pathology could be characterized with the parameters of Eqs. (2) and (3) that describe $P(t)$ and $U(t)$ (Lichtenhan *et al.*, 2005). To continue the development of a clinically useful technique that estimates surviving auditory nerve neurons in hearing impaired ears, in this study we apply the analytic CAP to click-evoked CAPs and examine the influence of temporary noise-induced hearing threshold shift (TTS) on human $P(t)$ and $U(t)$.

II. METHODS

A. Experimental subjects

Thirty-nine normal hearing human subjects were recruited from the greater Kansas City metropolitan area. CAPs could not be recorded on three subjects for some unknown reason and three additional subjects were used to acquire additional pilot data for click-evoked CAPs. The experiment reported here thus includes data from the right ear of 33 subjects: 27 subjects received noise exposure and 6 control subjects received a silent period in place of noise exposure. The median age of our subjects was 26 years, with a semi-interquartile range of three years. The minimum and maximum age of our subjects was 20 and 38 years, respectively. Twenty-nine females and seven males participated in the experiment. The normalcy of subjects' hearing status was evaluated by case history, otoscopy and pure tone audiometry (Grason Stadler GSI 61, Madison, WI), and tympanometry (GSI 33). All subjects had hearing thresholds at 0.25–8 kHz less than 25 dB HL, ear canal volume between 0.9 cm³–2.0 cm³, ear drum compliance between 0.30 mmhos and –1.70 mmhos, and middle ear pressure between 50 daPa and –100 daPa (Margolis and Hunter, 1999). Subjects were paid \$20.00 for their participation. All experimental procedures were approved by the Human Subjects Committee at KUMC (HSC No. 7881).

B. CAP evoking signal: Generation and delivery

Click-evoked CAPs were produced using a commercially available Bio-logic Traveler Express evoked potentials unit by delivering 100 μ s rectangular pulses to a Bio-logic insert earphone. The phase of every other click signal was alternated so that the cochlear microphonic was not recorded. Click signal levels ranged from 125 to 75 dB peak SPL (dB pSPL) decreasing in 10 dB steps and were presented at a rate of 11.1/s.

All stimuli were monitored with an Etymotic Research microphone system (ER-7C). The microphone probe tube was glued (Duro, Super Glue) to the silicone tubing of the tympanic membrane (TM) electrode. The microphone probe tube was attached in a manner so that the front end of the probe tube rested less than 8 mm from the TM to ensure that pressure nulls resulting from interaction between incident

and reflected acoustic waves of high frequency portions of our stimulus (i.e., 8–10 kHz) were negligible in the signal monitoring. The microphone signal was routed to a Tektronix oscilloscope (TDS 2014), Richardson, TX, where the level, time wave form, and spectral content were monitored.

C. CAP recording

CAPs were recorded with custom electrodes built according to Ferraro and Durant (2002) that were placed on the TM (noninverting). TeflonTM-insulated silver wire was cut to a length of about 2 in. and the ends of the wire were bared. Medical grade silicon tubing was cut to about 1½ in. and placed around the silver wire. The front end of the silver wire was hooked around a small wad of cotton that was soaked in Electrolyte Gel (Nicolet Biomedical) using a 1 cc syringe. The back end (i.e., the nontympanic membrane end) of the wire was attached to a copper microalligator clip that was in turn soldered to the end of an electrode cable. Gold-disk surface electrodes were attached to the low forehead (ground), and ipsilateral ear lobe (inverting).

Electrical signals were bandpass filtered between 100 and 3000 Hz (~12 dB/octave), amplified 200 000 times and digitized at 50 kHz. The artifact rejection was disabled for all recordings. Wave forms were displayed on a 10.24 ms time window yielding a wave form 512 points in length. Electroencephalic activity was monitored online to determine if subjects were physically calm and not producing excessive myogenic electrical artifact. Responses evoked from 125 and 115 dB pSPL were averaged from 1024 presentations; 2048 presentations were used for lower signal levels to improve the signal-to-noise ratio. Wave forms were saved to disk, converted to ASCII format using a Bio-logic program (ep2asci59), transferred to a personal computer suitable for data processing via 5.5 in. floppy disk, and then loaded into MATLAB (The Mathworks) for analysis.

D. Noise exposure

A 115 dB SPL narrow-band noise centered at 2 kHz was used for noise exposure intended to produce TTS. The noise was generated from a Madsen Electronics Clinical Audiometer (OB822), routed to an Optimus Stereo Amplifier (SA-155) and sent to the same Bio-logic headphone that delivered the click stimulus discussed earlier. The probe microphone tubing attached to the TM electrode was used to monitor the noise signal [Fluke Multimeter (8060A)].

The bandwidth of the noise was determined using an insert earphone positioned in a syringe with a 2 cc volume between the earphone and the syringe's rubber stopper. A probe tube from the ER-7C microphone system was placed at the rubber stopper. The microphone signal was sent to a Hewlett Packard Dynamic Signal Analyzer (3561A) and displayed in the frequency domain. The frequencies corresponding to the 3 dB "down points" of the narrow-band noise were 1630 and 2320 Hz.

The 2 kHz center frequency of the noise exposure stimulus was chosen because it is an octave below 4 kHz, which is the primary cochlear region that the click stimulates (Jerger and Mauldin, 1978; Bauch and Olsen, 1986, 1988;

Fowler and Mikami, 1992; Gorga *et al.*, 1985; Shepard *et al.*, 1992; Watson, 1996, 1999) and because Ward, Glorig and Sklar (1959) found a maximum temporary hearing loss occurs an octave above the characteristic spectral content of 100 dB SPL narrow-band noise stimuli. Moreover, it has been shown that narrow-band noise, as opposed to tonal, exposure did not produce as great a TTS, though it affected a wider range of hearing thresholds above the characteristic frequency (CF) of the noise exposure (Ward, 1962; Salvi *et al.*, 1983). In other words, narrow-band noise exposure produces a “flatter” or broader range hearing loss.

E. CAP analysis and curve fitting

CAP wave forms were digitally filtered in MATLAB using a high-pass cut off frequency of 150 Hz to decrease 60 Hz (and the 120 Hz harmonic) artifact. The high-pass filtering also reduced a low-frequency “voltage drift” appearing beyond the second peak of the CAP wave form, which most likely results from components of the auditory brain-stem response. After filtering, the CAP was fit with the analytic CAP using custom written software in TOMLAB (Tomlab Optimization), a constrained nonlinear least-squares fitting routine.

The TOMLAB fitting software allowed us to restrict the range over which analytic CAP parameters could vary, and improved the convergence of the fitting algorithm. The ranges were initially set according to realistic variations of normal, *in vivo* post-stimulus time histograms and single neuron action potentials (Kiang, 1965; Kiang *et al.*, 1976; Wang, 1979; Versnel *et al.*, 1990, 1992a, 1997). The lower boundary for β was set to 0.02 ms based on jitter measures from single neurons (Miller *et al.*, 1999). The upper boundary for parameter β was set to 8.5 ms based on the average maximum cochlear latency for humans of 7.5 ms (Eggermont, 1979) added to the maximum jitter for single neurons (Miller *et al.*, 1999). The lower and upper boundaries for α were defined as 0.6 and 7.5 ms, respectively, based on the minimum latency of high frequency derived band CAPs and maximum human cochlear latency (Eggermont, 1979; Schoonhoven *et al.*, 2001). Because our previous experience showed that N values below 0.01 were not statistically significant, our lower N boundary was defined as 0.01. Our upper N boundary was set to infinity.

The values of $U(t)$ parameters also remained adjustable in the curve fitting process because differences have been found between normal and pathologic single neuron action potentials (Prijs, 1986; Versnel *et al.*, 1992b). The lower boundary of parameter K was defined as 0.5 ms because we found it to improve the fit of the analytic CAP to physiologic CAPs. The upper bound of K was set to 2.0 ms based on a similar $U(t)$ model developed by McMahon and Patuzzi (2002). The lower and upper boundaries of $U(t)$ F were 500 and 2000 Hz; these values were chosen from data obtained by Versnel *et al.* (1992b), who fit separate Gaussian functions to the initial (negative) and second (positive) peak of recorded single neuron action potentials evoked from neurons having varying degrees of thresholds and spontaneous rates.

Parameter starting values and boundaries were provided to the TOMLAB software and the CAP parameters were estimated. Ninety-five percent confidence intervals for each parameter were computed. If a confidence interval included zero, the parameter was deemed insignificant and thus the entire model unuseable. In this case, the boundaries were adjusted and the curve fitting procedure repeated until significance ($p \leq 0.05$) for all parameters were obtained. The boundaries rarely had to be adjusted to any marked distance in order to obtain a model entailing all significant CAP parameters.

F. Experimental design

Following an initial hearing screening, subjects reclined in a single walled sound isolated room. Surface electrodes, TM electrode, with associated probe microphone, and insert ear phone were positioned. Prenoise exposure, CAPs were recorded in response to 125 to 75 dB pSPL clicks descending in 10 dB steps. Hearing threshold was subsequently acquired at 4 kHz and the subject was then exposed for 15 min to the narrow-band noise. Following noise exposure, 4 kHz hearing threshold was reexamined and postnoise exposure CAPs were recorded. TTS typically was determined about 30–60 s after cessation of noise exposure. The postnoise CAP recordings commenced about 60 s after the noise exposure ended. The order of postnoise click levels (e.g., 75–125 dB pSPL in 10 dB steps) was alternated between ascending and descending during postexposure CAP recordings for every other subject. Because hearing thresholds were recovering during postnoise recordings, we wanted to ensure that half of our low signal level data was acquired during peak TTS, and that half of our high signal level CAPs were as well recorded during the height of TTS in case there was an unexpected affect of signal direction. Postexposure CAP recordings took less than 30 min. Hearing threshold at 4 kHz was again determined at the conclusion of the experiment. The entire procedure including hearing testing, subject preparation for electrophysiological recording, and experimentation typically required 1.5–2 h.

G. Statistics

1. CAP parameter reliability

The interclass correlation coefficient (ICC) was used to measure the reliability of the curve fitting routine as well as the reliability of the physiologic responses. The ICC statistic was chosen over the Pearson coefficient, another reliability statistic, because a high Pearson correlation can exist even though the means differ between groups/sessions. *t*-tests are commonly used with Pearson correlation measures to determine if the means of independent and dependent variables differ. In contrast, the ICC accounts for both correlation and parameter size with one statistic. For the six control subjects not receiving noise exposure, CAPs were recorded before and after a 15 min silent period instead of the noise exposure and fit with the analytic CAP. ICCs were calculated for all six CAP parameters (β , α , N , K , and F), at each signal level before and after silent the period.

The ICC was defined as

$$ICC = \frac{MS_B - MS_W}{MS_B + MS_W}, \quad (4)$$

where MS_W is the average squared differences between each score within a session (e.g., average β for presilent period) and the group mean, and MS_B is the average squared differences between each recording condition (e.g., pre- and postsilent period β) mean and the grand mean.

2. CAP parameter growth function analysis

Hierarchical linear modeling [(HLM), Raudenbush and Bryk, 2002] was used to acquire the intercepts and slopes [i.e., π coefficients in Eq. (5)] of $P(t)$ and $U(t)$ parameter-signal-level functions for each subject and to also determine if hearing loss influenced these growth patterns. HLM describes each subject's growth trajectory and is more advantageous than other repeated measures statistics and ordinary least-squares regression because it does not require each subject to have data at each measurement interval, does not require fixed intervals between measures, and is more precise in coefficient estimation (Wu, 1996).

The level 1 HLM model

$$y = \pi_0 + \pi_1(SL) + \pi_2(SL^2) + e \quad (5)$$

was fit to each parameter-signal-level function for both pre- and postnoise data from all 33 subjects.¹ In Eq. (5) y is a given CAP parameter from Eq. (A1) (i.e., β , α , N , K , and F), SL is signal level, and e is a random error term. When a given term of Eq. (5) was insignificant, the model was reduced in a backward elimination approach (Mendenhall and Sincich, 2003). Equation (5) described the relationship between signal level and CAP parameters in a regression-like equation. A series of level 2 models,

$$\pi_0 = B_{00} + B_{01}(TTS) + r_0,$$

$$\pi_1 = B_{10} + B_{11}(TTS) + r_1,$$

$$\pi_2 = B_{20} + B_{21}(TTS) + r_2, \quad (6)$$

was fit to each parameter-signal-level function for the 27 subjects receiving noise exposure. In Eq. (6), TTS is the degree of temporary hearing loss at 4 kHz and r_n ($n=0,1,2$) is the random error. Insignificant coefficients of Eq. (6) were also reduced in a backward elimination approach until a model entailing all significant coefficients was found. When multiple significant models were found, chi-square tests were performed on deviance scores of the HLM models to determine the best model. Equation (6) described the influence of hearing loss on the level 1 coefficients. That is, Eq. (6) was used to characterize how the shape of the CAP parameter-signal level functions changed during TTS. A version of Eq. (6) not entailing B_{n1} ($n=0,1,2$) was fit to CAP parameter-signal-level function for each of the 33 subjects before noise exposure. All HLM coefficients were acquired using statistical software HLM 6 by Raudenbush *et al.* (2000).

FIG. 1. A histogram indicating the number subjects having a given degree of temporary threshold shift (TTS) measured at the cessation of noise exposure.

When the HLM did not show that the level 1 coefficients for a given CAP parameter varied significantly with hearing loss, paired samples t -tests were used on the pre- and post-noise exposure 75 dB pSPL CAP data from the 27 subjects receiving noise exposure. With the exception of $U(t)$ parameters F , t -tests² were performed on 75 dB pSPL CAP parameters because TTS is assumed to alter OHC physiology and it is at low signal levels where OHC feedback to the basilar membrane is responsible for the exceptional sensitivity in normal ears (Ryan and Dallos, 1975).

III. RESULTS

A. Hearing loss

Figure 1 is a histogram illustrating the number of subjects that acquired the various amounts of TTS at 4 kHz. The control subjects who did not receive noise exposure are not included in Fig. 1. The TTS distribution is positively skewed with a median of 15 dB and a semi-interquartile range of 5 dB. Hearing thresholds following noise exposure ranged from a 5 dB improvement to a 30 dB temporary loss. Consistent with typical 5 dB intratest reliability, six control subjects had no TTS, two had a 5 dB improvement, and one had a 5 dB temporary loss of hearing threshold.

Hearing threshold at 4 kHz was measured at the conclusion of the experiment immediately following the postnoise exposure CAP recordings. Time between cessation of noise exposure and the conclusion of the experiment was a positively skewed distribution (not shown) with a median of 20 min and a semi-interquartile range of 1.25 min. The distribution of threshold shifts at the conclusion of the experiment was normally distributed (not shown) with a mean of 6.67 dB (s.d. ± 5.18 dB).

B. Representative subjects

One subject's CAPs evoked from a 75 dB pSPL stimulus before and after noise exposure are shown in Fig. 2. The gray lines are the CAPs, and the solid black and dotted lines

FIG. 2. CAPs evoked from a 75 dB pSPL click stimulus for one subject (NH14) before (left panel) and after (right panel) noise exposure. Gray lines represent the CAPs and the solid and dotted lines represent the analytic CAP.

represent the analytic CAP. The $P(t)$ and $U(t)$ estimated from the Fig. 2 CAPs are shown in Fig. 3. In Figs. 2 and 3, the solid and dotted lines correspond to the before and after noise exposure model fits, respectively. Following noise exposure $P(t)$ had a shorter latency from stimulus onset as indicated by the smaller α parameter (cf. two numerical columns in the left panel of Fig. 3). The larger β value following noise exposure indicates that $P(t)$ increased in width and the smaller N following noise exposure indicates a reduction in the number of neurons contributing to the CAP. Following noise exposure $U(t)$ oscillated with a lower frequency and was less damped (i.e., “rang” more) as indicated respectively by parameters F and K .

C. Analytic CAP fit and reliability

Coefficients of determination (r^2) quantifying the goodness of fit between the analytic CAP and the physiologically recorded CAPs were acquired in MATLAB (CORRcoef). The analytic CAP fit favorably to prenoise, presilence, and post-noise CAPs (Fig. 4). The 33 subjects labeled as “Pre Noise” includes both the 27 noise exposed and 6 control subjects.³ A subtle difference existed between pre- and postnoise correla-

FIG. 4. Average (± 1 standard error of mean) Pearson correlations between the analytic CAP and physiologic CAPs as a function of signal level before (solid line) and after (dotted line) noise exposure. Control subjects are not included by postnoise data presented here.

tions at 75 and 125 dB pSPL though all correlations were still considered adequate.

The ICC calculation for CAP parameters acquired from control subjects’ recordings (i.e. pre- and postsilent period) provided reliability estimates of the CAP parameters (Fig. 5). Statistically significant ICCs lie above the solid gray line (0.669) and insignificant values lie below. The significance of a given ICC value was calculated from an F-test similar to that used in analysis of variance (ANOVA),⁴ where $F_{ANOVA} = MS_B / MS_W$ and MS_B and MS_W are the same as in Eq. (4). By rearranging to $MS_B = F_{ANOVA} MS_W$, and inserting into Eq. (4) yields $ICC = (F_{ANOVA} MS_W - MS_W) / (F_{ANOVA} MS_W + MS_W)$. Using an F_{ANOVA} value corresponding upper 5% of the F_{ANOVA} distribution and 5 degrees of freedom yielded the 0.669 value of the gray line.

As indicated by proximity to the gray line, most of the ICC coefficients were statistically significant, others just below the gray line were close to significance, and others far below the gray line were clearly not significant. We consider

FIG. 3. Post-stimulus time histogram [$P(t)$] (left) and single-neuron action potential [$U(t)$] (right) estimates derived from fitting the analytic CAP [Eq. (A7)] to CAPs of Fig. 2 before (solid line) and after (dotted line) noise exposure. $P(t)$ and $U(t)$ coefficients of Eqs. (2) and (3) are indicated within the respective graphs. Parameter N of Eq. (1) is given in the left panel.

FIG. 5. Interclass correlation coefficients [(ICC), Eq. (4)] for control subject CAP parameters of Eqs. (2) and (3) as a function of signal level acquired before and after a silent period. Given the degrees of freedom, the horizontal gray line indicates a significant ICC.

values just below the gray line to be reliable because the significance value (0.669) depends on degrees of freedom (i.e., sample size), which in our situation is low (i.e., $6-1=5$). The zero ICC values for CAP parameter F at 85 and 95 dB pSPL occurred because of limited between and within subject variability. Specifically, when the analytic CAP was fit to control subjects' physiologic CAPs the boundaries governing the range of the parameters was reached. This caused MS_B and MS_W to be zero and the resulting ICC to be zero.

D. $P(t)$ parameters

The mean and standard error of parameter β for each stimulus level is shown in Fig. 6 both before and after noise exposure. The solid and dotted lines are the HLM models fitted to the respective pre- and postnoise β data, the values of which are listed in Table I and II. The not applicable (NA) initials in Table I are place holders because the TTS level 2 HLM analyses were not performed on prenoise data. Before and after noise exposure β decreased nonlinearly with increases in signal level. The decrease was quadratic in nature, as indicated by the presence of significant B_{20} in both Tables I and II. Following noise exposure, neither the HLM intercept nor slope coefficients varied significantly with degree of hearing loss which is indicated by the zero value for B_{01} , B_{11} ,

FIG. 6. Poststimulus time histogram $[P(t)]$ "width" parameter β of Eq. (2) before (dark circles) and after (gray triangles) noise exposure as a function of signal level. Table I coefficients provided from the hierarchical linear modeling [(HLM), Eqs. (5) and (6)] of the prenoise β were used to construct the solid line. The dashed line represents the results of the postnoise HLM reconstructed from Table II coefficients.

and B_{21} in Table II. However, paired samples t -tests performed between pre- and postnoise β data (control subjects not included in prenoise data) from the lowest signal level indicated a significant difference ($t=-2.210$; $p=0.04$).

Similar to β , α decreased nonlinearly with increasing signal level both before and after noise exposure (top panel Fig. 7). In contrast to β , however, the α -signal-level HLM intercept and linear coefficient varied with degree of hearing loss following noise exposure (significant B_{01} and B_{11} terms in Table II). The intercept decreased as a function of degree of TTS, and is illustrated in the middle panel of Fig. 7, which plots the estimated values of π_0 from the HLM analysis for each subject as a function of TTS. In contrast, the linear coefficient (π_1) increased with TTS (bottom panel of Fig. 7, and Table II) though we chose to not fit a line to π_1 versus TTS because r_1 was not significant.

E. N parameter

The CAP parameter N increased nonlinearly with signal level (Fig. 8, left panel). As illustrated by the lack of significant B_{01} , B_{11} , and B_{21} terms in Table II, N did not vary with

TABLE I. Prenoise HLM coefficients

CAP parameter	π_0		π_1		π_2	
	B_{00}	B_{01}	B_{10}	B_{11}	B_{20}	B_{21}
β	-0.509 283	NA	0.003 649	NA	-0.000 093	NA
α	10.340 167	NA	-0.137 543	NA	0.000 533	NA
N	193.720 892	NA	-4.297 480	NA	0.024 417	NA
K	3.365 529	NA	-0.045 420	NA	0.000 248	NA
F	0.344 969	NA	0	NA	0.000 041	NA

TABLE II. Postnoise HLM coefficients.

CAP parameter	π_0		π_1		π_2	
	B_{00}	B_{01}	B_{10}	B_{11}	B_{20}	B_{21}
β	-0.350 634	0	0.014 054	0	-0.000 084	0
α	11.070 709	-0.030 202	-0.148 307	0.000 203	0.000 576	0
N	201.043 770	0	-4.592 246	0	0.026 745	0
K	0.933 861	0.010 056	0	0	0.000 031	0
F	0.338 681	0	0	0	0.000 036	0

degree of TTS. However, paired samples t -tests performed at 75 dB pSPL indicated a significant decrease in N following noise exposure ($t=3.679$; $p=0.001$).

F. $U(t)$ parameters

The K parameter, which governs the decay of $U(t)$, increased in a quadratic manner with increasing signal level both before and after noise exposure (top panel, Fig. 9). All K -signal-level HLM terms were significant before noise exposure (Table I), though only the intercept (B_{00}) and quadratic terms (B_{20}) were significant after noise exposure (Table II). Because of the small value of the quadratic term, the postnoise model fit to the data in the top panel of Fig. 9 appears to grow linearly. The significant B_{01} term in Table II indicates that the intercept of the K -signal-level function increased with degree of TTS following noise exposure. In the bottom panel of Fig. 9 are the values of π_0 as a function of degree of TTS estimated from the HLM analysis. The dotted line is the solution to Eq. (6) using coefficients from Table II.

Figure 10 indicates that the frequency of $U(t)$, parameter F , increased nonlinearly with signal level before and after noise exposure. As shown in Tables I and II, only the intercept (B_{00}) and quadratic term (B_{20}) of the HLM models were significant both before and after noise exposure, though neither of the terms were related to degree of TTS. When pre- and postnoise F was collapsed across signal level, however, a paired samples t -tests showed that that frequency of $U(t)$ oscillation was lower during TTS.

IV. DISCUSSION

A. Temporary hearing loss

The median TTS of 15 dB shown in Fig. 1 is consistent with the extensive literature review by Kryter (1970), who reported a 10–25 dB TTS from noise exposure similar to that used in our study. The mean 6.67 dB (s.d. ± 5.18 dB) threshold shifts at the conclusion of postnoise CAP recordings is essentially consistent with Kryter (1970), who cited reports of hearing thresholds from similar noise exposure that recovered to 5 dB of baseline after 20 min.

The nontonal, high-level, short duration noise exposure probably produced a TTS in our subjects that recovered monotonically. Ward *et al.* (1959) and Hirsh and Ward (1952) reported monotonic TTS recovery from similar noise exposures. The phenomenon commonly referred to as the “two minute bounce”—threshold elevation following the noise cessation, slight recovery near the first postexposure minute followed by maximum TTS around 2 min that then recovers monotonically—was reported by Hirsh and Ward (1952) for low frequency tonal exposure which differs from

FIG. 7. Top panel illustrates post-stimulus time histogram $[P(t)]$ “latency” parameter α of Eq. (2) before (dark circles) and after (gray triangles) noise exposure as a function of signal level. Table I coefficients obtained from HLM [Eqs. (5) and (6)] of prenoise α were used to construct the solid. The dashed line represents HLM coefficients of postnoise α from Table II coefficients. The middle panel shows the variation in the intercept of the α -signal level function with degree of threshold shift (TTS). The dotted line is the solution to Eq. (6) using values from Table II. The lower panel characterizes the behavior of the HLM linear term of the α -signal-level function as degree of TTS. The random error for the linear HLM term was not significant, and thus no scatter appears at the bottom.

FIG. 8. “Scaling” parameter N from Eq. (1) before (dark circles) and after (gray triangles) noise exposure as a function of signal level (left panel). Results of HLM [Eqs. (5) and (6)] reconstructed from Table I values are represented as the solid line and the postnoise HLM reconstructed from Table II values are represented as the dashed line. In the right panel is the same data as in the left panel, plotted on a log–log axis.

the noise exposure used here. On three separate occasions we measured the time course of one subject’s TTS recovery from the noise exposure used in this experiment and indeed did not find a two minute bounce.

B. $P(t)$ parameter β

Parameter β of Eq. (2) estimates the width of the summed *in vivo* probability density function describing the discharge timing of auditory nerve neurons (i.e., summed post-stimulus time histogram). In other words, β indexes

“compound neuronal synchrony.” Small β values indicate highly synchronous excitation of a population of neurons, whereas large values suggest less synchrony across neurons. In our study β decreased with increasing signal level suggesting greater synchrony of neuronal discharges at high signal levels. Additional components, however, could contribute to alterations in β with signal level. In their Fig. 10, Antoli-Candela and Kiang (1978) showed that increasing click level evokes post-stimulus time histogram peaks that occur before the tallest peak of single, high frequency nerve post-stimulus time histograms. The duration of the high-level peaks is narrower than the first peak from low-level click stimuli. Since the earliest components of the high-CF post-stimulus time histograms dominate the far-field recorded CAP (Kiang, 1965; Kiang *et al.*, 1976; Antoli-Candela and Kiang, 1978; Wang, 1979; Versnel *et al.*, 1990), these narrow peaks may explain our small β at high signal levels. Similarly, single neuron jitter—the standard deviation of single-neuron spike latency measures from multiple stimulus presentations (Miller *et al.*, 1999)—decreases with increasing electrical stimulus level in a nonlinear fashion akin to our β -signal-level function.

FIG. 9. Single-neuron action potential $[U(t)]$ “decay” parameter K from Eq. (3) before (dark circles) and after (gray triangles) noise exposure as a function of signal level (top panel). The solid line was reconstructed from Table I HLM [Eqs. (5) and (6)] coefficients of prenoise K . Similarly, the dashed line was obtained by solving the HLM Eq. (5) with values given in Table II. The circles in the bottom panel are the intercepts postnoise K -signal level functions—estimated from the HLM—vs TTS. The dotted line is the level 2 HLM function, i.e., Eq. (6).

FIG. 10. Single-neuron action potential $[U(t)]$ “frequency” parameter F from Eq. (3) before (dark circles) and after (gray triangles) noise exposure as a function of signal level. The solid line was constructed by solving the HLM Eq. (5) using Table I prenoise HLM coefficients. The dashed line is the postnoise F -signal-level function estimated from the HLM, the coefficients of which are in Table II.

A significant paired samples t -test performed between pre- and postnoise β values evoked from 75 dB pSPL clicks indicates that $P(t)$ was wider during TTS. This conflicts with a report by Versnel *et al.* (1997), who showed narrower single neuron click-evoked post-stimulus time histograms from ears having permanent noise induced threshold shift, and with reports by Salvi *et al.* (1979, 1983) showing no alteration to the post-stimulus time histogram. The discrepancy between our findings and that of Versnel *et al.* and Salvi *et al.* may be explained by the anatomical differences resulting from temporary and permanent hearing loss which may ultimately manifest differently in cochlear physiologic measures. A TTS producing noise exposure leads to bending and separating of stereocilia tips in the third OHC row (Gao *et al.*, 1992) and ultimately to disarticulation with the tectorial membrane (Nordmann *et al.*, 2000). In contrast, noise exposure causing permanent threshold shift can be associated with complete loss of OHCs and buckling of the pillar bodies (Nordmann *et al.*, 2000). Versnel *et al.* (1997) swiftly conjectured that narrow post-stimulus time histograms evoked from ears with permanent hearing loss result from healthy inner hair cell responses during initial deflections of the basilar membrane impulse response. We here elaborate on our interpretation of the short narrative of Versnel *et al.* The initial basilar membrane deflections do not depend on OHC health, though the impulse response wave form illustrates that the basilar membrane vibration transitions into a condition that is dependent on OHC health during later deflections [e.g., Fig. 4, Ruggero and Rich (1991)]. The basilar membrane's impulse response wave form has a low instantaneous frequency during initial deflections and "glides" into a higher vibrational pattern that corresponds to the characteristic frequency place (Shera, 2001a)—a behavior that is independent of signal level and is controlled by the OHCs (Shera, 2001b). Unlike the TTS case in our experiment where OHCs are probably present (Gao *et al.*, 1992) though have altered physiology, absent OHCs in cases of permanent hearing loss would result in a quicker decaying (shorter lasting) basilar membrane impulse response which would thus narrow post-stimulus time histograms to an extent described by Versnel *et al.* (1997).

C. $P(t)$ parameter α

The parameter α from Eq. (2) describes the time delay from stimulus onset to $P(t)$ onset. A linear function fit to the quadratic α -signal-level function of the top panel in Fig. 7 approximates a decrease in α of ~ 1.5 ms from 125 to 75 dB pSPL. Such estimates in latency shifts are consistent with the nearly $-30 \mu\text{s}/\text{dB}$ for the first peak of the human CAP (Durant and Ferraro, 1999). That is to say, $P(t)$ onset latency varies as a function of signal level decays at about the same rate as the human CAP.

The significant B_{01} and B_{11} in Table II indicate that the intercept and linear term of the α signal level varied with degree of TTS. For individuals with greater amounts of TTS, the α -signal-level function decreased at all signal levels and became more linear. This effect is only minimally noticeable in the top panel of Fig. 7 because individual TTS effects are

FIG. 11. α -signal-level functions constructed from HLM coefficients of Table II using the TTS level 2 independent variable [Eq. (6)] varying from 5 to 30 dB. Iso-intensity plots for 75 dB pSPL α (stars) and 125 dB pSPL (cross hair circle) derived from data of the top panel are shown in the bottom panel.

not noticeable in the mean data. Figure 11 more systematically demonstrates changes in the α -signal-level function for various degrees of TTS. In Fig. 11 the α -signal-level functions were reconstructed from the coefficients of Table II and by varying the independent variable of Eq. (6) (i.e., TTS; 5–30 dB). The large gray arrow emphasizes that a shorter α was acquired during TTS and the amount of shift was related to the degree of TTS. Moreover, comparing the data identified by the star versus cross hairs shows that a greater shift occurred at low intensity levels. Iso-intensity plots in the bottom panel of Fig. 11 acquired from the 75 dB pSPL (stars) and 125 dB pSPL (cross haired circles) extremes of the top panel functions illustrate that α was more at 75 than at 125 dB pSPL.

Shorter response latency during TTS is consistent with Chertoff *et al.* (1996), who used cochlear microphonic recordings to construct a third-order polynomial describing mechano-electric transduction. During TTS the polynomial coefficients showed a phase lead, or shorter latency, suggesting that responses came from a more basal location. Simi-

larly, CAPs have been shown by Eggermont (1979) to have a shorter latency in hearing impaired subjects as a result of the broadening of cochlear filters following damage. In other words, a reduction in the steepness of the high frequency side of damaged neurons' frequency tuning curves presumably allows responses to stimuli from higher frequencies than CF, thus producing shorter latencies than in the normal case.

Shorter response latency in the presence of outer hair cell damage is not a pervasive finding in the literature, however. High intensity stimuli have been shown to yield normal CAP latencies in animals with permanent outer hair cell damage (Wang and Dallos, 1972; Salvi *et al.*, 1979; Versnel *et al.*, 1997). The disparity between our findings and those reports of normal latency following outer hair cell damage may be because negative damping provided by the outer hair cells is negligible at high signal levels and inner hair cells may respond at high stimulus levels independent of outer hair cell status. Because TTS most likely results from OHC alteration (Gao *et al.*, 1992; Nordmann *et al.*, 2000), it is not surprising that responses from the lower signal levels were more affected by TTS than the higher signal levels as it is at low levels where OHC physiology is influential.

D. Parameter N

According to the theoretical CAP model proposed by Goldstein and Kiang (1958), the N parameter represents the number of neurons contributing to the CAP. If so, then the nonmonotonic increase in Fig. 8 indicates that the number of neurons contributing to the CAP increased with signal level. This is consistent with the finding that the number of single neuron responses increases with signal level (Kiang, 1965; Versnel *et al.*, 1992a).

The HLM analysis showed that the prenoise N -signal-level function had a quadratic coefficient greater than zero, which indicates a nonlinear growth with signal level. Others have reported a similar trend in the growth of CAP amplitude with signal level (e.g., Teas *et al.*, 1962; Portmann *et al.*, 1973; Montandon *et al.*, 1975; Özdamar and Dallos, 1976; Crowley, 1976; Thornton, 1976; Ino, 1976; Versnel *et al.*, 1992a), though others have reported that the CAP amplitude growth function had a negative quadratic term suggesting a compressive growth (e.g., Benítez *et al.*, 1972; Yoshie, 1976; Thornton, 1976; Eggermont *et al.*, 1976; Don and Eggermont, 1978; Salvi *et al.*, 1983). Obvious differences between the various reported growth function could be due to data transformations such as the use of log-log versus linear-log axes. In fact, plotted with log-log axes in the right panel of Fig. 8 N appears to grow somewhat compressively at the midsignal levels. Perhaps this subtle indication of compressive growth would be more apparent had we recorded additional data below 75 dB pSPL.

The positive quadratic growth of the N -signal-level function could be due to our electrode position. Varying electrode position around the neural generators can affect the profile of the CAP amplitude growth function (Yoshie and Ohahi, 1969), as well as the profile of the single neuron action potential (Kiang *et al.*, 1976; Stegeman *et al.*, 1979).

The profile of our N -signal-level function could also be related to the frequency content of the click stimulus and the CF for which the TM electrode is most sensitive. Monitoring the ear canal signals (see Sec. II) showed that after passing through the outer ear canal, most of the click energy was around 4 kHz. Four-thousand kilohertz could possibly be below the CF of the cochlear frequency place for which the TM electrode is most sensitive. In a similar off-CF stimulation condition, auditory nerve neurons show a positive quadratic growth function plotted on linear-log axes. Our results could thus reflect the off-CF auditory nerve property that is reviewed by Kiang (1965), Pickles (1988), Ruggero (1992), and Harrison (2001).

Neither the intercept (π_0), linear (π_1), nor quadratic (π_2) coefficients significantly varied with degree of hearing loss. However, paired samples t -tests showed that parameter N evoked from the lowest signal level was significantly smaller during TTS indicating fewer neurons discharged during TTS. Temporary noise-induced alterations to outer hair cell physiology most likely contributed to the reduction of N during TTS. A reduction in negative damping would decrease the low intensity gain provided to the basilar membrane and consequently provide less input to the inner hair cells and associated afferent neurons. The lack of influence of TTS on N at higher levels, probably occurred given that outer hair cell feedback is negligible at high stimulus levels (Robles and Ruggero, 2001).

E. $U(t)$ parameters K and F

The K parameter of Eq. (3) governs the decay of $U(t)$. Small K values result in a $U(t)$ profile having less damping while large values of K result in a quickly damped $U(t)$. That is to say, small K values force the single neuron action potential estimate to "ring" longer than large values of K . The top panel of Fig. 9 shows that $U(t)$ had greater damping as signal level increased in both the prenoise and postnoise cases. The large standard error of K means seen in the top panel of Fig. 9 is consistent with other reports of large inter- (Kiang *et al.*, 1976; Wang, 1979) and intra- (Prijs, 1986) subject variability in the profiles of the single neuron action potential obtained from spiked triggered averaging. The coefficients from the HLM analysis were significant both before and after noise exposure despite the variability. Moreover, the intercept increased after noise exposure and the increase was proportional to degree of hearing loss indicating less oscillations in $U(t)$ wave forms in subjects with large amounts of TTS. This finding is further illustrated in Fig. 12, where K -signal-level functions were reconstructed by using coefficients provided in Table II and by varying the independent variable of Eq. (6) (i.e., TTS; 5–30 dB). The functions shift to larger values of K in direct relation to the degree of TTS.

Parameter F of Eq. (3) governs the oscillatory frequency of our single neuron action potential estimate. A lower F value indicates a slower oscillation of the $U(t)$ wave form for a given unit of time. Figure 10 shows that the $U(t)$ oscillation increased about one octave from 0.5 to 1 kHz over the range of 75–125 dB pSPL. Furthermore, although a change in

FIG. 12. Parameter K -signal-level functions constructed from HLM [Eqs. (5) and (6)] coefficients of Table II using the TTS level 2 independent variable [Eq. (6)] that varied from 5 to 30 dB.

F -signal-level function was not related to degree of TTS, t -tests performed on the F parameter before and after noise exposure showed that $U(t)$ had a lower frequency of oscillation during TTS.

Despite the assumption of the analytic CAP that the $U(t)$ profile is everywhere constant throughout various characteristic cochlear frequency places (Kiang *et al.*, 1976; Wang, 1979), the situation in damaged cochleae is probably different (Prijs, 1986; Versnel *et al.*, 1992b). Various explanations may account for the changes in $U(t)$ as a result of signal level and TTS. One interpretation could be that the single neuron action potential was altered during TTS due to alterations in neuron physiology, as there is some evidence that the single neuron action potential can change in animals with noise-induced hearing loss (Versnel *et al.*, 1992b). However, there are alternative explanations that need to be examined in future experiments. For example, the $U(t)$ profile may have been altered due to the basal-ward spread of excitation— inherent with increasing signal level—which stimulates neurons residing closer to the TM electrode. Indeed, it has been shown that alterations in the distance from source location to the recording location can change the $U(t)$ profile (Stegeman *et al.*, 1979). Another alternative explanation is that a change in $U(t)$ was due to a limitation of the analytic approach because the chosen $P(t)$ function has only one maximum and can thus not represent post-stimulus time histograms with multiple maxima. The decaying exponential function used for $U(t)$ may have resultantly varied to account for the additional extrema in post-stimulus time histograms.

F. Clinical implications

The ultimate goal of our group's research is to develop clinical tools to identify the locus of lesion(s) and characterize the pathophysiology in ears with sensory-neural hearing loss. Currently available clinical tests are limited in this regard. For example, audiological diagnostics cannot distinguish between hearing loss arising from impairment of the stereocilia, OHC body, stria vascularis, afferent auditory nerve neurons, or impaired K^+ ion current throughout various regions within the cochlear partition. Accurate identi-

cation of site of lesion(s) in cases of profound impairment must certainly be known before the promising stem cell or genetic therapies can be applied. Moreover, improved descriptions of pathophysiology of surviving cochlear structures could lead to improved hearing aid and cochlear implant processing algorithms.

Toward our ultimate goal, we have developed a battery of tests that describe cochlear function by using cochlear microphonics (Chertoff *et al.*, 1996, 1997, 2003; Bian and Chertoff, 1998, 2001), summating potentials (Choi *et al.*, 2004), and otoacoustic emissions (Bian *et al.*, 2002, 2004; Krishnan and Chertoff, 1999). Each of these tests has the potential to assist in localizing the site of lesion(s) and in describing pathophysiology in cases of sensory-neural hearing loss. It is in the context of this more comprehensive test battery that we foresee using the analytic CAP. With approaches similar to that reported with the experiments of this manuscript, much of our previous work has aimed at describing the pathophysiology of sensory-neural hearing loss. The aim of our future work is important, as we will relate attributes of this test battery to anatomical lesions verified with histological analyses.

G. Summary and conclusions

Fitting the analytic CAP to physiologic CAPs evoked from human ears provided estimates of the parameters of $P(t)$ and $U(t)$. HLM quantified changes in the CAP parameters as a function of signal level both before and after noise exposure. As click level increased, β decreased indicating a narrowing in the width of $P(t)$. Following noise exposure β was larger for the lowest click levels suggesting a wider $P(t)$ which was related to less synchronous responses. The $P(t)$ latency parameter, α , decreased with increasing signal level and was shorter at all signal levels following noise exposure. Alterations in α values indicated that CAPs were dominated by responses from neurons located more basal-ward as signal level increased and after noise exposure. Parameter N increased with signal level and was smaller after noise exposure at the lowest signal level. Postnoise N changes imply that responses from fewer neurons were evoked at the lowest click level during TTS. Both the damping and frequency parameters of $U(t)$ increased with signal level. For large amounts of TTS, $U(t)$ from low click levels had greater damping than before noise exposure. Additionally, $U(t)$ oscillation was lower in frequency at all click intensities following noise exposure. The changes in $U(t)$ could be due to alterations in the single-neuron action potential, relative distance from source to electrode, or limitations of the equation used to describe $P(t)$.

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APPENDIX: DERIVATION OF THE ANALYTIC CAP

This derivation of the analytic CAP using functional forms of $P(t)$ and $U(t)$ was initially reported by Chertoff (2004) and is repeated here. The analytic CAP is given as

$$\text{CAP}(t) = N \int_{-\infty}^t P(\tau) U(t - \tau) d\tau, \quad (\text{A1})$$

where

$$P(t) = \left(\frac{t - \alpha}{\beta} \right)^{\gamma-1} e^{-((t+\alpha)/\beta)} \quad (\text{A2})$$

and

$$U(t) = e^{-kt} \sin(\omega t). \quad (\text{A3})$$

In the Laplace domain, Eq. (A1) can be expressed as

$$\text{CAP}(s) = NP(s)U(s). \quad (\text{A4})$$

Similarly, $P(t)$ and $U(t)$ are expressed as

$$P(s) = \frac{e^{-s\alpha}(1/\beta)^{\gamma-1}\Gamma(\gamma)}{(s + 1/\beta)^{\gamma}} \quad (\text{A5})$$

and

$$U(s) = \frac{\omega}{(s + k)^2 + \omega^2}. \quad (\text{A6})$$

Setting $\gamma=2$, substituting Eqs. (A5) and (A6) into Eq. (A4), and converting Eq. (A4) to the time domain via the inverse Laplace transform (MAPLE 7.0), Waterloo, Ontario, Canada, yields

$$\begin{aligned} \text{CAP}(t) = & -\frac{N\beta H(t - \alpha)}{c^2} \{ \omega e^{-((t+\alpha)/\beta)} [c(t - \alpha) - 2\beta(\beta k \\ & - 1)] + e^{-k(t-\alpha)} [-a \sin(\omega(t - \alpha)) - b \cos(\omega(t \\ & - \alpha))] \}, \end{aligned} \quad (\text{A7})$$

where

$$a = \beta\omega^2 - (\beta k - 1)^2,$$

$$b = 2\beta\omega(1 - \beta k),$$

$$c = \beta^2\omega^2 + (\beta k - 1)^2,$$

$$H = \text{Heaviside}.$$

¹HLM π coefficients of Eq. (5), a mere symbol, should not be confused with the numerical value π of Eq. (3).

²The student's t in the name t -tests should not be confused with the time variable t of Eqs. (1)–(3).

³The number of subjects in Fig. 4 is indicated by the letter n , not to be confused with CAP parameter N of the analytic CAP.

⁴The letter F in the name F_{ANOVA} should not be confused with the CAP parameter F of Eq. (3).

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