The influence of noise exposure on the parameters of a convolution model of the compound action potential

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The influence of noise exposure on the parameters of a convolution model of the compound action potential (CAP) was examined. CAPs were recorded in normal-hearing gerbils and in gerbils exposed to a 117 dB SPL 8 kHz band of noise for various durations. The CAPs were fitted with an analytic CAP to obtain the parameters representing the number of nerve fibers (N), the probability density function [$P(t)$] from a population of nerve fibers, and the single-unit waveform [$U(t)$]. The results showed that the analytic CAP fitted the physiologic CAPs well with correlations of approximately 0.90. A subsequent analysis using hierarchical linear modeling quantified the change in the parameters as a function of both signal level and hearing threshold. The results showed that noise exposure caused some of the parameter-level functions to simply shift along the signal level axis in proportion to the amount of hearing loss, whereas others shifted along the signal level axis and steepened. Significant changes occurred in the $U(t)$ parameters, but they were not related to hearing threshold. These results suggest that noise exposure alters the physiology underlying the CAP, some of which can be explained by a simple lack of gain, whereas others may not.

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I. INTRODUCTION

Sensorineural hearing loss results from anatomical changes in the cochlea and auditory nerve. One problem with this type of hearing loss is that damage to the cochlea and auditory nerve varies greatly among patients (Schuknecht, 1988), and clinical techniques that distinguish and quantify the anatomical changes are lacking. Although audiometric threshold measurements are clinically valuable, they fail to provide sufficient information regarding underlying cochlear pathologies and neural integrity (e.g., see Salvi *et al.*, 1983). New techniques that distinguish sensory from neural pathologies and that also estimate the extent of anatomical damage would be useful in the clinical setting to provide a site of lesion as hair cell regeneration and genetic therapy are developed and may perhaps drive advancements in signal processing of hearing aids and cochlear implants.

By studying physiological components of the compound action potential (CAP), it might be possible to develop an assay of neural integrity in the presence of sensory and/or neural hearing loss (e.g., see Hall, 1990). Because its properties reflect the time-delayed sum of neural discharges, the CAP can be described as the convolution of a probability density function and a single-unit waveform. As proposed by Goldstein and Kiang (1958),

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

where $P(t)$ represents a probability density function of single-unit discharges from a population of neurons, $U(t)$ represents a single-unit waveform recorded extracellularly, and N is the number of neurons contributing to the CAP.

Equation (1) has been used successfully to model the CAP waveform. For example, Wang (1979) recorded $U(t)$ from an electrode on the round window using a spike-triggered averaging technique. $P(t)$ was obtained from post-stimulus time histograms from single auditory nerve fibers with a wide range of characteristic frequencies. Convolution of $P(t)$ and $U(t)$ produced a simulated CAP similar to the CAP recorded by an electrode on the round window. The results of Wang (1979) are similar to those of other investigators who used the spike-triggered averaging technique (Versnel *et al.*, 1992a) as well as modeling approaches of the CAP (de Boer, 1975). Minor variations between model CAPs and physiologic CAPs, however, do exist but are limited to the later peaks in the CAP waveform. Together, the results from the previous studies indicate that the convolution model [Eq. (1)] is a reasonable description of the relation between single-unit events and the whole-nerve CAP.

Equation (1) has also been used to obtain $P(t)$ and $U(t)$, given a recorded CAP. Using a recorded CAP and assumed $U(t)$, Elberling (1976) derived $P(t)$ by deconvolving the CAP by $U(t)$. Chertoff (2004) obtained $P(t)$ and $U(t)$ in Eq. (1) by convolving functional forms for $P(t)$ and $U(t)$ and fitting the results to recorded CAPs. $P(t)$ was defined as

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

for $t \geq \alpha$, 0 otherwise. Parameter t is time and α represents the time delay from the stimulus onset to the onset of the CAP. When $\gamma=2$, $P(t)$ reaches its maximum at $t-\alpha=\beta$. Beta also influences the width of $P(t)$. The unit waveform was given as

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

where K was the decay constant and $\omega=2\pi F$. The analytic solution was fitted to recorded CAPs, and the parameters describing $P(t)$ and $U(t)$ were examined as a function of stimulus frequency and signal level. The results showed that α decreased with increasing signal level, suggesting a spread of excitation to fibers with high characteristic frequencies, and N and β (at 2, 4, 8, and 16 kHz) increased with signal level, illustrating a change in the number of fibers and synchrony among auditory nerve fibers contributing to the CAP.

One could envision that cochlear and/or neural damage could lead to changes in N , $P(t)$, or $U(t)$. Some damage may result in changes to the CAP that can be quantified with conventional measures such as amplitude and latency, whereas others may not. For instance, as inner hair cells die and the pillar cells collapse, auditory nerve fibers degenerate (Morest *et al.*, 1998). A reduction in the number of auditory nerve fibers should reduce the amplitude of the CAP and also decrease the magnitude of parameter N of Eq. (1). In contrast, if the timing of discharges among auditory fibers is altered, e.g., becoming less synchronous, it may be reflected in the summed probability density function as a widening of width of $P(t)$. Similarly, alterations in ionic conductance or changes in myelin due to genetic abnormalities or disease processes may affect $U(t)$. Importantly, some of these alterations may affect the auditory threshold and may manifest themselves only at certain signal levels or, perhaps, as signal level changes. The long-term goal of this investigation is to determine if the parameters of the convolution model of the CAP, and their change as a function of signal level, can be used as an assay of the extent of neural damage. The purpose of this study was (1) to determine if the CAP convolution model could adequately fit CAPs recorded from animals with peripheral auditory damage and (2) to determine if alterations in the growth functions of the model parameters could be explained by elevations in the hearing threshold.

II. METHODS

A. Subjects, animal preparation, and data acquisition

The CAP data from 40 animals used in this study were from Chertoff *et al.* (2003). Thus the stimuli, surgical methods, and data acquisition are only briefly explained. CAPs were collected from Mongolian gerbils (*Meriones unguiculatus*) weighing between 40 and 60 g. Once hearing was confirmed to be within normal limits using auditory brainstem responses (ABRs), the animals were assigned to either a control ($n=6$) or experimental group ($n=34$) to receive noise exposure for durations of either 0, 1, 1.5, 2, 4, 8, 16, 64, or 128 h. The noise exposure signal was a 3 kHz bandwidth

noise centered at 8 kHz and presented at 117 dB SPL. After exposure, ABRs were recorded weekly for up to 7 weeks or until a permanent hearing loss was confirmed. For CAP recordings, animals were sedated with Nembutal (64 mg/kg), the bulla was opened, and an electrode was placed on the round window. A secondary electrode was inserted into the neck musculature and served as ground. Body temperature was maintained at 37 °C using a heating pad with a rectal thermometer (Harvard). CAPs were recorded to 2 ms tone bursts (1, 2, 4, 8, and 16 kHz) windowed within a $\cos^2$ function, yielding a 1 ms rise/fall time. The signal level started at 100 dB SPL and descended in 5 dB steps until 15 dB SPL. All acoustic signals were created in an array processor (Tucker-Davis Technologies, TDT). The electrophysiologic signals were amplified 5000 times (Stanford SR560 Steward VBF10), filtered (0.03–25 kHz), digitized (TDT, AD2), averaged, and stored on disk for offline analysis. A CAP consisted of at most 500 signal presentations. All animal protocols were approved by the University of Kansas Medical Center Institutional Animal Care and Use Committee.

B. Curve fitting

The analytic CAP (Chertoff, 2004) was fitted to all recorded CAPs (in millivolts) using a constrained nonlinear least squares fitting routine (TOMLAB). Lower and upper bound limits were imposed on the convolution model parameters to improve the convergence of the fitting algorithm and provide a unique solution. $P(t)$ required boundary conditions for two parameters: β and α ; gamma was set to 2 and was not a free parameter. For β , the lower boundary was set to 0.02 ms and was based on the minimum jitter of a single neuron [Miller *et al.* (1999), Fig. 5(b)]. The maximum value was set to 2.4 ms and includes the maximum jitter [~ 1.0 ms, Miller *et al.* (1999)] and the cochlear delay of 1.4 ms for the 12 mm section of the gerbil cochlea. The minimum value for α was set to 1 ms and represents the delay of the acoustic tube connecting the headphone to the ear canal. The maximum value was chosen to be 5 ms.

In addition to varying the $P(t)$ parameters, the parameters of $U(t)$ were also allowed to vary in this study. Our motivation was to allow for the variation in the amplitude and time between peaks that was reported by Wang (1979). The boundaries for the frequency parameter, F , were determined from the data Tables I and II of Versnel *et al.* (1992b) who considered the width of the initial negative peak (σ_n) and the subsequent positive peak (σ_p) of $U(t)$ to be the standard deviation of a Gaussian function fitted separately to each peak. From their Tables I and II, we chose the values of $\sigma_n=0.15 \pm 0.10$ ms and $\sigma_p=0.23 \pm 0.12$ ms for the width of the two peaks because of the large number of nerve fibers used to estimate these values. The lower and upper boundaries of F were defined as $F_l=[3(\sigma_n+0.10+\sigma_p+0.12)]^{-1}$ and $F_u=[3(\sigma_n-0.10+\sigma_p-0.12)]^{-1}$, respectively, where F_l and F_u are the lower and upper frequencies in kilohertz. The 3 in these equations represent three standard deviations of the Gaussian distribution. The calculated values for the boundaries were $F_l=0.555$ kHz and $F_u=2.083$ kHz and were rounded to $F_l=0.5$ kHz and $F_u=2.0$ kHz. The boundaries for

TABLE I. Coefficient values for N -level growth functions, goodness of fit, and variability among animals.

Frequency (kHz)	A_0	B_0	A_1	B_1^a	A_2^a	A_3^a	R^2	σ
16	0.796	-0.087	0	0.778	0	0	0.859	0.094
8	1.240	-0.150	0.048	1.300	-0.776	0.003	0.886	0.109
4	-4.152	-0.017	0.195	0	-2.733	0.013	0.869	0.112
2	-4.394	0	0.142	0	-1.478	0.005	0.934	0.060
1	-4.475	0	0.137	0	-1.413	0.005	0.947	0.038

^aValues $\times 10^{-3}$.

the decay constant of $U(t)$, i.e., K , were set to 0.5 ms for a lower boundary and to 2.0 ms for an upper boundary. The 0.5 ms value was chosen because it improved the fit of the analytic CAP to the physiologic CAP recorded at the highest signal level. The 2 ms upper boundary value was based on model $U(t)$ using an exponentially decaying sine function by [McMahon and Patuzzi \(2002\)](#). The boundaries for N were set to a minimum of .001 because our previous experience ([Chertoff, 2004](#)) showed that values below this were not statistically different from zero. The maximum N was chosen to be infinite. Because we did not scale $U(t)$ and we fit the CAP in units of millivolts, N is a dimensionless scalar that, according to the model, should change when the number of nerve fibers contributing to the CAP changes.

Initial starting values for the parameters and boundary values were provided to the constrained nonlinear optimization routine (TOMLAB), and CAP parameters from Eqs. (1)–(3) were estimated. Using the Jacobian of the parameters and the residuals between the fit and the physiologic CAP, standard errors and confidence intervals for each parameter were obtained. If any of the CAP parameters were not statistically significant (i.e., if the confidence interval included zero), the initial parameters were varied and the curve fitting repeated. This procedure was repeated until statistically significant parameters were obtained. Using the constrained procedure, we were able to obtain statistically significant parameters at signal levels that were lower than our previous study ([Chertoff, 2004](#)). The parameters analyzed as a function of signal level and auditory threshold in this study were all statistically significant at $p < 0.05$.

The covariation of parameters and accuracy of the curve fitting was examined by creating simulated CAPs using all possible combinations of five values for each of the five parameters resulting in 3125 CAPs. Each simulated CAP was fitted with the analytic CAP, and the resulting parameter values were compared to the actual parameters used to create the simulated CAPs. In no instance did the change in one parameter influence or correlate with the change in another parameter, suggesting independence of the parameters. Error in the curve fitting procedure was estimated by $\text{error} = ((\text{act} - \text{pred})/\text{act})100$. The maximum error was 0.5% and was associated with the parameter K .

C. Data analysis

The goal was to obtain a mathematical description for the influence of signal level and auditory threshold on each CAP parameter's growth function (i.e., parameter-level func-

tion). The parameter-level functions were fitted with a polynomial equation having coefficients that varied as a function of hearing threshold. That is,

$$\log_{10} Z(x, y) = \sum_{n=0}^3 C_n x^n, \quad (4)$$

$$C_n = A_n + B_n y,$$

where Z is a given CAP parameter, C_n is a polynomial coefficient, x is the signal level in dB SPL and y is the hearing threshold in dB SPL. Hearing threshold was defined as the average CAP threshold at 4, 8, and 16 kHz and will be referred to as pure tone average (PTA). These frequencies were chosen because this was the frequency range where the majority of hearing loss was present. A threshold was defined as the lowest signal level at which a CAP could be visually detected.

As indicated in Eq. (4), C_n depends on A_n and B_n , which are to be determined from the data. This was accomplished using hierarchical linear modeling (HLM) ([Raudenbush and Bryk, 2002](#)) and the statistical software HLM 6 hierarchical linear and nonlinear modeling ([Raudenbush et al., 2000](#)). HLM was chosen instead of ordinary least squares regression because HLM uses an empirical Bayes estimation procedure (also known as shrinkage estimators) or a maximum likelihood approach to estimate the coefficients for each animal. These estimates are more accurate than ordinary least squares when sample sizes differ, which is an inherent condition in our study because animals differed in their thresholds after noise exposure and hence differed in the number of data points used in the estimate of the coefficients. The average value of the coefficients is reported in Tables I and II.

For an initial analysis, Eq. (4) with an intercept (C_0) and linear coefficient (C_1) were used to fit the logarithm of a CAP parameter to the signal level. Additional higher-order terms were added sequentially if they significantly improved the fit ($p < 0.05$). Only terms that were statistically significant were included in the complete model, and the best model was defined as the one with the lowest deviance score ([Raudenbush and Bryk, 2002](#)).

To determine if Eq. (4) provided an adequate description of the data for each animal, a coefficient of determination (R^2) was computed. This was accomplished by obtaining a "predicted" growth function for each animal using an animal's own coefficients (i.e., slope, intercept, etc.). The predicted growth function was correlated with the animal's ac-

TABLE II. Coefficient values for α -level growth functions, goodness of fit, and variability among animals.

Frequency (kHz)	A_0	B_0	A_1	B_1^a	A_2^a	R^2	σ
16	0.206	0.011	-0.010	0	0	0.909	0.146
8	0.223	0.008	-0.007	0	0	0.888	0.206
4	0.313	0.007	-0.008	0	0	0.919	0.141
2	0.466	0	-0.005	4.800	-3.800	0.969	0.024
1	0.490	0	-0.005	2.900	-4.300	0.972	0.020

^aValues $\times 10^{-5}$.

tual data. The R^2 value from each animal was averaged across all animals for each of the stimulus frequencies. The mean and variance of R^2 are reported in the tables.

III. RESULTS

A. Hearing threshold

A relevant issue for determining the relation between the hearing threshold and the change in the parameter-level functions is the amount of variation in hearing thresholds. To adequately derive a relation, it is important to have a wide range of thresholds. This was accomplished in our previous study (Chertoff *et al.*, 2003) by exposing animals to different durations of noise. The PTAs of the animals used in the analysis for the present study are illustrated in Fig. 1 and show the range of hearing thresholds from normal hearing to hearing thresholds as high as approximately 95 dB SPL.

B. Fit of the CAP convolution model

Previously, the convolution model of the CAP was shown to adequately fit physiologically recorded CAPs from normal-hearing animals (Chertoff, 2004). In the present study, we were interested in determining if the fit varied with signal level and the amount of hearing loss. The dependent variable in the analysis was the correlation between the analytic CAP and the physiologic CAP, and the independent variables were signal level and PTA. Equation (4) was used

for the analysis with a slight modification; the correlation value was considered on a linear scale (i.e., not logarithm). The coefficients were estimated by HLM. The mean (± 1 SD) correlation coefficients are illustrated in Fig. 2. For the majority of signal levels and frequencies, the correlation values were above 0.9. The HLM analysis indicated that a small cubic polynomial trend occurred across the signal levels for each frequency, but the coefficients did not vary with PTA, indicating that the fit of the analytic CAP to the physiologic CAP was not related to the amount of hearing loss.

C. Representative animals

Figure 3 illustrates recorded CAPs (gray lines) and analytic CAPs (black lines) to a 16 kHz tone burst for a gerbil from the control group (left panel) and the noise-exposed group (right panel) at 100 dB SPL. In both animals, the analytic CAPs fitted the recorded CAPs quite well, with coefficients of determination (i.e., R^2) of 0.86 and 0.87, respectively. There were, however, differences between the normal and noise-exposed animal. The CAP from the noise-exposed animal was smaller (notice the change in the scale of the figure) than that from the normal animal, and the first negative peak was slightly delayed compared to the delay in the normal animal.

These changes were reflected in the parameters of Eq. (1)–(3) (Fig. 4). N was smaller in the noise-exposed animal and increased at a faster rate with signal level than in the normal animal. The delay parameter α showed a similar lin-

FIG. 1. PTA thresholds computed from 4, 8, and 16 kHz for each animal in this study. The open symbols represent the animals that did not receive noise exposure. The filled symbols are PTAs from noise-exposed animals.

FIG. 2. Symbols represent the mean correlation computed from all of the animals between the analytic CAP and the physiologic CAPs. The error bars indicate ± 1 standard deviation.

FIG. 3. CAPs from a control (left panel) and noise-exposed animal (right panel). Gray lines are the physiologic recorded CAPs, and the black lines are the analytic CAPs. PTA is the average CAP threshold at 4, 8, and 16 kHz. The fits between the physiologic CAPs and analytic CAPs are indicated by R^2 .

ear trend with signal level between the two animals. However, the noise-exposed animal's delay was shifted to longer delays.

Other changes in the parameters of $P(t)$ and $U(t)$ occurred, although they were not immediately apparent in the

CAP waveforms of Fig. 3. Beta was smaller in the noise-exposed animal and, in contrast with the control animal, decreased with increasing signal level. K , the decay parameter of $U(t)$, remained constant for many of the signal levels but then decreased at the highest level in the control animal. No trend in the K -level function was found for this noise-exposed animal. In the normal animal, F , or the frequency of $U(t)$, rose quickly from ~ 800 to ~ 950 Hz and then remained constant as the signal level increased. A similar trend was noted for the noise-exposed animal although the overall value of F was reduced.

D. Parameter N

The influence of the signal level on N is illustrated in Fig. 5. For the control group (dashed lines), the growth functions were similar among animals. Given the log-log axis, N grew linearly at low signal levels and saturated at high signal levels. By contrast, the noise-exposed animals (solid lines) were less homogeneous than the control animals. At high frequencies (16, 8, and 4 kHz), the growth functions shifted to higher sound pressures, and in some cases (16 and 8 kHz),

FIG. 4. The change with signal of the parameter values from Eqs. (1) and (2) [$P(t)$, top panels] and Eq. (3) [$U(t)$, bottom panels] for the two animals presented in Fig. 3. The stimulus was 16 kHz. Dashed lines indicate the control animal, and the solid lines indicate the noise-exposed animal.

FIG. 5. The change in N with signal level for the control group animals (dashed lines) and noise-exposed animals (solid lines). Each line represents one animal's N -level function.

the functions steepened. For low frequencies (2 and 1 kHz), N changed similarly for both the control and noise-exposed groups.

Figure 6 illustrates the solution to Eq. (4) using each animal's coefficients. Equation (4) fitted the data well; R^2 ranged from a low of 0.86 at 16 kHz to a high of 0.95 at 1 kHz with a small variance among animals. The good fit of Eq. (4) to the data indicates that some of the variability in the N -level functions in the noise-exposed animals can be accounted for by the hearing threshold. For example, the best fit to the 16 and 8 kHz data required the intercept (C_0) and linear term (C_1) to vary as a function of PTA. As shown in Table I (average value of the coefficients), C_0 decreased (i.e., a negative B_0) and C_1 increased (i.e., a positive B_1) with an increase in PTA. For both frequencies, the decrease in C_0 with PTA indicated that the N -level functions shifted along the signal level axis in animals with elevated thresholds. Moreover, the greater the threshold elevation, the greater the shift. The increase in C_1 with PTA indicated that as hearing loss became more severe, the slope of the N -level function steepened. By contrast, at 4 kHz, only the intercept (C_0) decreased as a function of PTA. Thus for many of the animals, the N -level growth function remained in the same shape even as hearing loss became more severe. The N -level function simply shifted along the signal level axis in an amount proportional to PTA. For the lower frequencies (2 and 1 kHz), PTA did not significantly contribute to the polynomial description of the N -level function. Thus, a third-order polynomial equation with constant coefficients described these N -signal level functions.

E. Parameter α

The delay parameter of $P(t)$, α , changed with signal level and the shape of the α -level functions varied with fre-

FIG. 6. Estimated N -level functions using Eq. (4) with the coefficients from each individual animal. Control animals are indicated by dashed lines, and noise-exposed animals are represented by solid lines.

quency (Fig. 7). In both the control and noise-exposed groups α decreased with increasing signal level for the 4, 8, and 16 kHz signals. At 1 and 2 kHz, a slight curvature in the α -level function was present. Similar to N , a greater variation in the growth functions occurred for the noise-exposed animals than the control animals. In the noise-exposed group, the functions showed longer delays in the high frequencies (16, 8, and 4 kHz) and less curvature in the functions for the low frequencies as compared to the control animals.

Much of the variation in the noise-exposed group could be described by Eq. (4). Figure 8 shows the predicted α -level functions. The fit of Eq. (4) to each animal's data was slightly higher than N , with an R^2 that ranged from a low of 0.89 at 8 kHz to a high of 0.97 at 1 kHz. The variation among animals was small (SD of R^2 ranged from 0.02 to 0.12). Table II shows that at 4, 8, and 16 kHz the best fit to the data was a linear function (on a log-log scale) with an intercept (C_0) that varied with PTA, indicating that the α -level functions shifted to larger delays as PTA increased (positive B_0). By contrast, at 1 and 2 kHz, the linear term (C_1) of the concave-downward quadratic functions increased with PTA (positive B_1), demonstrating that the slope of the α -level function decreased as PTA increased.

FIG. 7. The change in α as a function of signal level for the control (dashed lines) and noise-exposed animals (solid lines).

F. Parameters β , K , and F

Equation (4) provided a poorer description of the influence of hearing threshold on the growth functions for β , K , and F compared to those for the other parameters. R^2 ranged from a low of 0.21 for β at 1 kHz to a high value of 0.64 for F at 1 kHz. The average standard deviation in the fit of Eq. (4) to the parameter-level function among animals was larger than N and α . In some conditions the standard deviation was as large as the average R^2 , indicating wide variation in the ability of Eq. (4) to describe the parameter-level functions from the animals. Thus, instead of describing the relation between the hearing threshold and the growth functions, we examined if the parameters from normal-hearing animals differed from hearing-impaired animals. The animals were divided into two groups; those with PTAs ≤ 30 dB SPL were considered to have normal hearing and those with PTAs > 30 dB SPL were to have hearing loss. This cut point was determined from our database of CAP thresholds in normal animals from our laboratory. The parameters were evaluated at two signal levels; 100 dB SPL and signal level at the threshold. Independent t -tests were computed between the normal-hearing and hearing-impaired animals for each frequency. The type I error was controlled by dividing 0.05 by five comparisons, thus providing a conservative p value for statistical significance (i.e., 0.01). Levene's test of homogeneity was used to examine the assumption of equal variability, and if significant, individual group variances and an adjusted degree of freedom were used for the t -test (SPSS version 15).

Beta was larger in the hearing-impaired animals than in the normal-hearing animals for the 4, 8, and 16 kHz stimuli (Fig. 9) at both signal levels, reaching statistical significance only at the threshold signal level. At 1 and 2 kHz, there was

FIG. 8. Predicted α -level functions from Eq. (4) using each animal's coefficients. Dashed and solid lines indicate control and noise exposed animals, respectively.

no difference between the two groups at either signal level. For the parameters F and K there were some minor effects of hearing loss. At 16 kHz only, F increased from an average of 879 Hz in normal-hearing animals to 1077 Hz in impaired animals ($p=0.004$). The parameter K was larger in the hearing-impaired animals as compared to the normal-hearing animals at 1 kHz, but only for the threshold signal level ($p=0.004$). The difference was 0.355 ms.

IV. DISCUSSION

A. Convolution model

The first goal of this investigation was to determine if the analytic CAP fitted well to the physiologic CAPs in

FIG. 9. Parameter β at 100 dB SPL (left panel) and at the threshold signal level (right panel). Filled circles are for animals with PTAs ≤ 30 dB SPL, and open circles are for animals with PTAs > 30 dB SPL. The error bars represent the standard error of the mean.

noise-damaged animals and to examine the influence of signal level and hearing threshold. The analytic CAP fitted the physiologic CAPs with correlation values that were generally larger than 0.90 across most of the signal levels. Moreover, the fit of the analytic CAP did not vary with the amount of hearing loss. This indicates that on average, the analytic CAP described a large proportion (88% R^2 , collapsed across levels and frequencies) of the variance in the CAP waveform morphology, independent of the amount of hearing loss. Although subjective, we felt that the correlations were large enough to consider the analytic CAP a good description of the physiologic CAP.

B. Parameter N

Parameter N grew nonlinearly with signal level (log-log scale) for the majority of frequencies (1, 2, 4, and 8 kHz). The functions grew steeply at low and high signal levels and were compressive at middle signal levels. This growth pattern is reminiscent of the nonlinear growth pattern of the basilar membrane with signal level (Robles and Ruggero, 2001). For 1 and 2 kHz tone burst stimuli, a significant third-order polynomial equation was required to fit the growth functions. The coefficients did not vary with the degree of hearing loss, indicating that high frequency hearing loss did not alter the low frequency N -level functions. At 4 kHz, the growth functions were altered by noise exposure. The best fit to the data was a third-order polynomial equation with an intercept that varied with the degree of hearing loss. This indicates that the N -level functions were not altered in shape but simply shifted horizontally. This suggests that after the signal level reaches the threshold, auditory nerve fibers contributing to the CAP respond with a growth function similar to that seen in animals with normal auditory sensitivity. That is, the change in the growth function appears to be caused by a simple lack of gain. The growth functions for both the 16 and 8 kHz stimuli also required coefficients that changed with the degree of hearing loss. Both the intercept and linear terms were related to the auditory threshold. The intercept decreased with hearing threshold, representing a shift along the signal level axis, and the linear term increased proportionally with animals' PTAs, indicating that the greater the hearing loss the steeper the N -level functions. A steeper slope is consistent with some reports on the input-output function of the amplitude of the N1 of the CAP in noise-exposed animals (Elberling and Salomon, 1976; Salvi *et al.*, 1983; Wang and Dallos, 1972) and humans with sensorineural hearing loss (Yoshie and Ohashi, 1969; Portmann *et al.*, 1973). However, these reports are by no means conclusive, as other investigators reported no change in the slope or a decrease in the slope in the N1-amplitude functions (Popelar *et al.*, 1987; Dolan and Mills, 1989).

The increase in the slope of the high frequency (i.e., 8 and 16 kHz) N -level functions in hearing-impaired animals suggests a recruitmentlike phenomenon. This could result from the broadening of the basilar membrane tuning following noise exposure, leading to the excitation of fibers from remote cochlear regions. Other mechanisms for recruitment, as discussed by Heinz *et al.* (2005), include an increase in

FIG. 10. (Color online) N -level values at 8 kHz plotted as a function of sensation level (i.e., dB above threshold). The solid thick line is the average N value (± 1 SD) computed across the control animals, and the gray lines are the data from each of the noise-exposed animals. The circle illustrates the region where animals show steeper growth functions than the control animals.

the discharge rate of auditory nerve fibers or a compression in the threshold distribution of auditory nerve fibers. However, analyzing a population of auditory nerve fibers from noise-exposed cats, Heinz *et al.* (2005) found no evidence for an increase in the discharge rate of individual fibers or change in the threshold distribution of auditory nerve fibers. They did report that a spread of excitation could occur, but this was limited to high signal levels. This is consistent with our results where animals with the largest hearing losses tended to have steeper slopes. Another possibility, however, is that the N -level functions at 16 kHz were actually nonlinear and compressive in a shape similar to 4 kHz. In the statistical fitting procedure for the normal animals, the linear fit may have been dominated by the compressive nature of the function, resulting in a shallow slope. For animals with high thresholds, the nonlinear compressive curve would shift to the right due to elevated thresholds. A shift to the right would decrease the influence of the compressive portion of the function and would highlight the linear (low-level) portion. The statistical fitting would now be influenced by the steep linear portion of the function and would result in an erroneous steep slope. To examine this possibility we examined the N -level functions at 8 kHz as a function of sensation level (SL), i.e., decibel above the threshold. Figure 10 illustrates the average (± 1 SD) N -level function from the control animals along with the data from the animals exposed to noise. For signal levels ranging from 0 to 20 dB SL, some of the animals show steeper growth functions than the normal-hearing animals, supporting the statistical analysis. Future studies with more signal levels, however, would help clarify the distinction between actual recruitment and a simple shift along the threshold axis.

C. Parameter α

The delay parameter of $P(t)$, α , decreased as the signal level increased. For the high frequency stimuli (4, 8, and

16 kHz), α decreased linearly (log-log axis). To compare the change in α with signal level to previous studies, we fit a linear regression line to the nonlinear growth functions described by Eq. (4) and Table II. The slope of these functions were similar to those reported by Burkard *et al.* (1993) who reported a slope of -0.0117 ms/dB at 8 kHz, and our data indicates (from Table II) a slope of -0.0106 ms/dB.

Noise exposure altered the growth functions by shifting the intercepts of the functions by an amount proportional to the amount of hearing loss. It is interesting to note that the coefficient A_1 in Table II ($A_1 = -0.010$) is approximately the negative of the coefficient B_0 ($B_0 = 0.011$). This suggests a relation, and perhaps a common mechanism, between the change in the latency of the CAP with signal level and the shift in the latency of the CAP with the degree of hearing loss (i.e., slope relating C_0 to PTA). Heil and Neubauer (2001) proposed that auditory nerve fibers are triggered in response to the temporal integral of the pressure envelope of an acoustic signal. The integration of pressure by auditory nerve fibers may account for the relation between the latency of the CAP with signal level and the amount of the shift in the α -level function with threshold elevation. If the envelope of a signal is given as $P_a(t) = P_s \sin^2(\pi t / 2t_r)$, where P_s is the peak pressure of the stimulus, t is the time, and t_r is the rise time of the stimulus, then the threshold, θ , is defined as $\theta = \int_0^D P_a(t) dt$, where D is the delay of the CAP. Assuming that auditory nerve fibers respond at the peak of the stimulus when the signal level is at the threshold, then, as shown in the Appendix, the delay of the CAP $\approx c(P_{th}/P_s)^{1/3}$, where P_{th} is the sound pressure at the threshold, P_s is the stimulus sound pressure, and $c = 0.85$. This equation shows that the delay of the CAP with signal level is a family of curves shifted by the pressure at the threshold. On a log-log scale the delay-level function would decrease with a slope of $1/3$ for both normal-hearing and hearing-impaired animals, but the curves would be shifted to longer delays in the hearing-impaired animals. The shift would be related to the degree of hearing loss, and a plot of the shift as a function of pressure at threshold would yield a slope of $1/3$. This suggests that temporal integration could account for the similarity between the slope of the α -level function (A_1) and the shift of the α -level function with PTA (B_0).

The data from our study can be used to obtain a function similar to that proposed by the temporal integration of the sound pressure model. As shown in the Appendix, $\alpha \approx a(P_{th}/P_s)^{1/5}$, where a is ~ 2.0 . The slope of the α -level function is equal in magnitude to the shift of the α -level functions with PTA. However, the slope is $1/5$ instead of $1/3$. Thus, although temporal integration may account for the equal magnitude of the slope of the α -level function and of the C_0 -PTA function from our data, it does not account for the actual slopes. It is possible that an additional component to the temporal integration model may be necessary to modify the exponent.

At 1 and 2 kHz, there was a significant quadratic component to the α -level function, and as PTA increased, the linear term of the quadratic function increased. This caused the concavity of the α -level function to decrease with increasing auditory threshold. A likely explanation is that the

CAP to low frequencies includes a larger cochlear traveling wave delay component compared to the CAPs to high frequencies, and responses from animals with high thresholds have an initial delay due to hair cell damage in the basal end of the cochlea. That is, at high signal levels the latency of the 2 kHz CAP in normal animals is similar to that at 16 kHz, indicating a common basal cochlear place of origin. As signal level decreases, the 2 kHz response shifts to its “best frequency” region in the cochlea. In animals with high thresholds, there is damage to the basal part of the cochlea, causing an initial apical shift in α to a region of functioning hair cells and neurons. The subsequent shift in α with signal level to the 2 kHz place will therefore be less than that in normal-hearing animals.

The literature regarding the influence of hearing loss on the latency-level function of N1 is conflicting. In guinea pigs with kanamycin induced hearing loss, Wang and Dallos (1972) showed no effect of the hearing loss on the latency-intensity function of N1. Similarly, Berlin and Gondra (1976) reported normal N1 functions in humans with sensorineural hearing loss of 25–55 dB. In contrast, Yoshie and Ohashi (1969) reported a parallel shift in the latency-level functions in damaged ears, which is consistent both with our results and with Elberling and Salomon's (1976) data from subjects who had a large degree of high frequency hearing loss. It is possible that the contrasting literature is due to the type of hair cells damaged, and the extent of hearing loss. The animals from Wang and Dallos' (1972) study had missing outer hair cells (OHCs) and normal inner hair cells (IHCs). In Berlin and Gondra's (1976) patients, the hearing loss was believed to be due to noise exposure, and with the limited extent of hearing loss reported, it is likely that this influenced only OHCs. Remaining IHCs could be stimulated by stereocilia being driven by fluid coupling in the organ of Corti (Nowotny and Gummer, 2006). Thus the latency of the response would be normal. In contrast, if both OHCs and IHCs were damaged, as we believe in our study because of the long duration noise exposures, an additional elevation in threshold would occur. More time would be required to integrate neurotransmitters before auditory nerve fibers would respond and, along with a shift to remote cochlear regions, could result in a shift in the latency-level function.

D. Parameters β , F , and K

The influence of the hearing threshold on the growth of β with signal level was not accurately described by the power function in Eq.(4). This could reflect a limitation in the power function chosen to fit the growth function or it may indicate that changes in β with signal level are not related to the degree of hearing loss. Beta was larger at the high frequencies in animals with hearing loss as opposed to normal-hearing animals. The trend was apparent at 100 dB SPL but only reached statistical significance for signal levels at the threshold. This indicates that the width of $P(t)$ was larger in impaired animals than in normal animals and suggests a decrease in the synchrony of discharges from auditory nerve fibers contributing to the CAP. A decrease in synchrony could result from a change in the location of the

fibers contributing to the CAP. That is, given that the latency of auditory nerve fibers is $\approx 1/\text{CF}$ (Kiang, 1965), where CF is a nerve fiber's characteristic frequency, the synchrony among apical fibers is different from that among basal fibers. If the fibers that are dominating the CAP in impaired ears are located more apically than normal ears, then less synchronous responses among auditory fibers could occur and lead to an increase in β .

Similar to β , the fit of Eq. (4) to the parameters of $U(t)$ was quite variable among animals. However, some effects of hearing loss on the $U(t)$ parameters occurred when evaluated at two different signal levels. Because $U(t)$ is a volume conducted extracellular triphasic waveform (Stegeman *et al.*, 1979) that is related to the intracellular potential of a nerve fiber (Clark and Plonsey, 1968), various explanations could account for the change in $U(t)$. Speculatively, these include a change in the distance between the source of the CAP and the recording site, alteration in the homogeneity of the conductive medium due to mixing of cochlear fluids after damage, and, perhaps, changes to ion channels in surviving nerve fibers causing an alteration in the action potential. More detailed physiologic experiments will be needed to understand the changes in $U(t)$ in pathologic ears.

E. Clinical implications

The research presented in this paper is part of an ongoing research to develop clinical diagnostic procedures that identify the locus of auditory damage and describe the pathophysiology underlying sensory-neural hearing loss in humans. As future stem cell and genetic treatments are developed, it will be important to have clinical techniques that identify the locus and extent of insult in order to appropriately target therapeutic intervention. The results of this study showed that the convolution model of the CAP fitted well the CAPs from both normal-hearing and noise-exposed animals, and a quantitative relation between the signal level and the hearing threshold was obtained. This was in agreement with the findings of Lichtenhan and Chertoff (2008), which showed that the convolution model could also be fitted to CAPs recorded from humans using an electrode placed on the eardrum both before and after noise exposure. This is encouraging as a first step in translating our animal findings to human application. Interestingly, some of the parameters changed similarly between the two studies. For example, β increased and N decreased at low signal levels after noise exposure in both studies. However, the parameter α decreased after noise exposure in the human subjects, whereas it increased in the animal subjects. This may be due to the different exposure frequencies used in the two studies, 2 kHz versus 8 kHz narrow-band noise, and differences in the mechanisms of temporary and permanent hearing loss. For a continued development of the parameters into a clinical tool, future research will be required to determine the relation between the changes in the parameters and the changes in the anatomy of the auditory nerve, as well as attempt to determine if the parameters can distinguish cochlear from neural damage.

V. CONCLUSIONS

The high correlations between the analytic CAP and the physiologic recorded CAPs indicate that the convolution model of the CAP provides an adequate description of CAP waveform morphology.

The growth functions of the CAP parameters N and α are well described by a polynomial equation with coefficients that depend on the hearing threshold. In some cases the variation of the coefficient with the hearing threshold indicated that noise exposure resulted in a simple lack of gain, whereas in other cases the slopes of the functions were altered.

The growth functions of the parameters β , F , and K were not adequately explained by a polynomial function with coefficients that varied with the hearing threshold. However, the parameters did change as a result of noise exposure and were suggestive of a decrease in synchrony in discharges among auditory nerve fibers and perhaps changes in either the source or the volume conduction properties of the medium from which the CAP is recorded.

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APPENDIX

1. Temporal integration of sound pressure and CAP latency

The purpose of this Appendix is to illustrate the following two points. First is to show that if the latency of the CAP depends on the temporal integration of sound pressure (i.e., similar to auditory nerve fibers, Heil and Neubauer, 2001), then the latency-intensity function can be approximated by a power function. Second is to show that the slope of this function on a log-log scale is the same as the slope relating CAP latency to elevations in auditory threshold.

Given that the envelope of our signal is $P_a(t) = P_s \sin^2(\pi t / 2t_r)$, where P_s is the peak pressure of the stimulus and t_r is the rise time of the stimulus, then the threshold is defined as

$$\theta = \int_0^D P_a(t) dt, \quad (\text{A1})$$

where D is the delay from the stimulus onset. Substituting in the functional form of $P(t)$ from above and solving the integral yield

$$\theta = P_s \left[\frac{D}{2} - \frac{t_r}{2\pi} \sin\left(\frac{\pi D}{t_r}\right) \right], \quad (\text{A2})$$

with units of Pa s. In our data, the threshold is defined in pascals. If we assume that at threshold the auditory nerve responds at the peak of the stimulus, then the delay of the

CAP from the stimulus onset due to temporal integration would equal the rise time (t_r). Therefore, if $D=t_r$, then

$$\theta = P_{th} \left[\frac{t_r}{2} - \frac{t_r}{2\pi} \sin(\pi) \right] \quad (A3)$$

or

$$\theta = \frac{P_{th} D}{2}, \quad (A4)$$

where P_{th} is the pressure at the threshold. The rise time of the signals in this study was 1 ms; therefore $\theta=0.5P_{th}$. Using this relation and rearranging Eq. (A2) allow us to examine the relation between the delay of the CAP, threshold, and stimulus pressure. That is,

$$\frac{P_{th}}{P_s} = 2 \left[\frac{D}{2} - \frac{t_r}{2\pi} \sin\left(\frac{\pi D}{t_r}\right) \right]. \quad (A5)$$

To show that this equation provides a function that is approximately linear on a log-log scale, we let $k=t_r/\pi$, and rearranging we find

$$D - k \sin\left(\frac{D}{k}\right) = \frac{P_{th}}{P_s}. \quad (A6)$$

Expanding Eq. (A6) in a Taylor series in D/k and retaining the lowest order give

$$D \approx c \left(\frac{P_{th}}{P_s} \right)^{1/3}, \quad (A7)$$

where $c=0.85$. Equation (A7) shows that the CAP delay is a family of curves that on a log-log axis would have the same slopes of $-1/3$ but shifted along the delay axis. A plot of the shift of the functions with a change in threshold would yield a slope of $1/3$.

2. CAP latency

A similar function as B7 can be derived from the HLM analysis of α . From Eq. (4) and $\alpha=Z$,

$$\log_{10} \alpha(x,y) = C_0 + C_1 x, \quad (A8)$$

where

$$C_0 = A_0 + B_0 y,$$

$$C_1 = A_1.$$

x is the signal level in dBSPL and y is PTA in dBSPL. Thus,

$$\alpha = 10^{A_0 + B_0 y + A_1 x}. \quad (A9)$$

Now $SPL=20 \log_{10}(P_s/P_0)$ and $PTA=20 \log_{10}(P_{th}/P_0)$, where P_s , P_{th} , and P_0 are pressures in pascals for the stimulus, stimulus level at threshold, and reference pressure (0.000 02 Pa), respectively. Therefore,

$$\alpha = 10^{A_0} \left(\frac{P_{th}}{P_0} \right)^{B_0(20)} \left(\frac{P_s}{P_0} \right)^{A_1(20)}, \quad (A10)$$

and at 16 kHz, $A_0=0.206$, $B_0=0.011$, and $A_1=-0.010$ (Table II). Equation (A10) can be rewritten as

$$\alpha = a \left(\frac{P_{th}^{0.22}}{P_s^{0.20}} \right) \quad (A11)$$

or

$$\alpha \approx a \left(\frac{P_{th}}{P_s} \right)^{1/5}, \quad (A12)$$

where $a=1.9952$. Similar to Eq. (A7), on a log-log axis, α would show that the magnitude of the slope relating α to the signal level would equal the slope relating α to the threshold. However, the slopes obtained from the data are smaller than predicted by a temporal integration of the sound pressure model for CAP latency.

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