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Cochlear toughening, protection, and potentiation of noise-induced trauma by non-Gaussian noise

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An interrupted noise exposure of sufficient intensity, presented on a daily repeating cycle, produces a threshold shift (TS) following the first day of exposure. TSs measured on subsequent days of the exposure sequence have been shown to decrease relative to the initial TS. This reduction of TS, despite the continuing daily exposure regime, has been called a cochlear toughening effect and the exposures referred to as toughening exposures. Four groups of chinchillas were exposed to one of four different noises presented on an interrupted (6 h/day for 20 days) or noninterrupted (24 h/day for 5 days) schedule. The exposures had equivalent total energy, an overall level of 100 dB(A) SPL, and approximately the same flat, broadband long-term spectrum. The noises differed primarily in their temporal structures; two were Gaussian and two were non-Gausssian, nonstationary. Brainstem auditory evoked potentials were used to estimate hearing thresholds and surface preparation histology was used to determine sensory cell loss. The experimental results presented here show that: (1) Exposures to interrupted high-level, non-Gaussian signals produce a toughening effect comparable to that produced by an equivalent interrupted Gaussian noise. (2) Toughening, whether produced by Gaussian or non-Gaussian noise, results in reduced trauma compared to the equivalent uninterrupted noise, and (3) that both continuous and interrupted non-Gaussian exposures produce more trauma than do energy and spectrally equivalent Gaussian noises. Over the course of the 20-day exposure, the pattern of TS following each day's exposure could exhibit a variety of configurations. These results do not support the equal energy hypothesis as a unifying principal for estimating the potential of a noise exposure to produce hearing loss. [DOI: 10.1121/1.1531981]

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I. INTRODUCTION

The role of temporal variables in a noise exposure paradigm has taken on a new level of interest since (a) Miller *et al.* (1963) and Clark *et al.* (1987) showed that threshold shifts (TS) following a noise exposure could be modulated by a cyclic pattern of exposure and (b) the discovery of the motor process associated with the outer hair cell (OHC) system (see Brownell, 1990 for a review). The reduction in TS following daily repeated exposures to the same noise has been called toughening (TS_R). That is, threshold shifts following each day's exposure are reduced despite the continuing exposure. Toughening, while dependent on the level and spectrum of the stimulus Subramaniam *et al.*, 1991), has been shown to occur as a result of interrupted exposures to continuous octave bands of noise (Boettcher *et al.*, 1992; Subramaniam *et al.*, 1992) as well as from broadband impact noise exposures with peak SPLs over 125 dB (Hamernik and Ahroon, 1998). The ability of the auditory system to produce a TS_R seems to be dependent on an intact OHC system and is not affected by large inner hair cell (IHC) losses (Abroon and Hamernik, 2000; Hamernik *et al.*, 1998).

Another demonstration of the effects that the temporal variables of a noise exposure can have on the cochlea is provided by experiments showing that for the same exposure energy and spectrum, noise-induced trauma is a function of the kurtosis statistic (β), where kurtosis is defined as the ratio of the fourth-order central moment to the squared second-order central moment of the amplitude distribution. That is, non-Gaussian continuous noise exposures are more traumatic than are Gaussian exposures having equivalent energy and spectra. The increased hazard increases as β increases (Lei *et al.*, 1994; Hamernik and Qiu, 2001). Temporal effects, such as those described above, affect the applicability of current standards for predicting the hazard posed by excessive noise exposures such as the ISO-1999 (ISO, 1990) document. This standard incorporates an energy-based evaluation of an exposure. An energy metric is, however, insensitive to temporal factors.

The experimental results presented here show that: (1) Exposures to interrupted high-level, non-Gaussian signals produce a toughening effect comparable to that produced by an equivalent interrupted Gaussian noise. (2) Toughening, whether produced by Gaussian or non-Gaussian noise, results in reduced trauma compared to the equivalent uninterrupted noise, and (3) both continuous and interrupted non-Gaussian exposure produce more trauma than do energy and spectrally equivalent Gaussian noises.

II. METHODS

Thirty-six chinchillas (between 1- and 2-years old) were used as subjects. Each animal was made monaural by the

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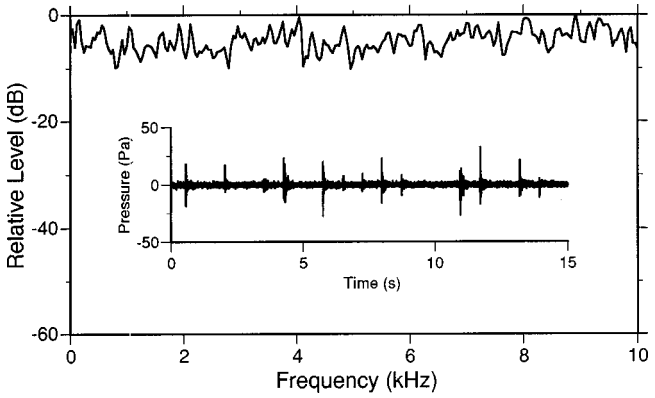

FIG. 1. The average spectrum obtained from eight 40-s samples of the digitized noise waveform. The spectrum was approximately the same for each of the four noise exposures. The inset shows a 15-s sample of the pressure-time waveform of a non-Gaussian exposure. Peak SPLs and inter-impact intervals were randomly varied.

surgical destruction, under anesthesia, of the left cochlea. During this procedure a bipolar electrode was implanted, under stereotaxic control, into the left inferior colliculus and the electrode plug cemented to the skull for the recording of auditory evoked potentials (AEP). The AEP was used to estimate pure-tone thresholds, and surface preparations of the organ of Corti were used to estimate the IHC, OHC populations. Additional details of the experimental methods, beyond those presented below, may be found in Ahroon *et al.* (1993).

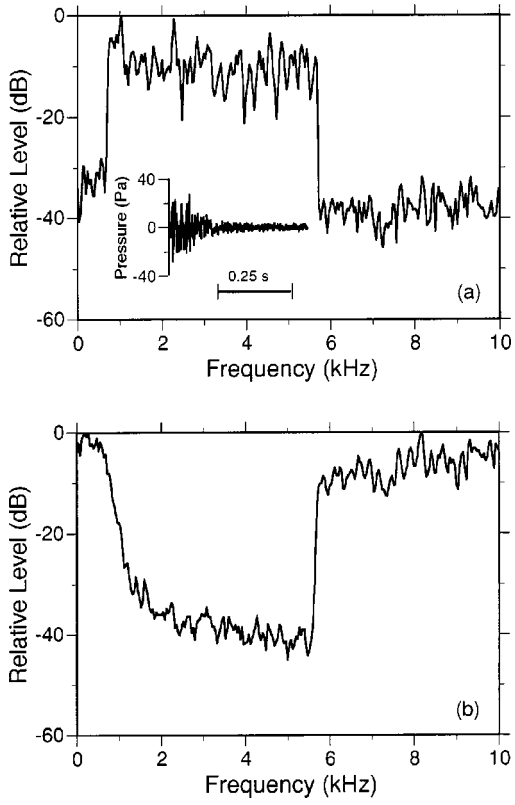

FIG. 2. (a) The spectrum of one of the impacts that was used to create the character of the non-Gaussian noise exposure. The insert shows an impact waveform. (b) The spectra of the complementary Gaussian noise that was mixed with the impact stimuli to form the non-Gaussian noise with kurtosis $\beta=33$.

TABLE I. Octave band SPL (dB) averaged over eight 40-s samples of the digitized waveform for the four exposure conditions.

Octave band cf (kHz)	G-5/20d	NG-5d	NG-20d
0.50	89	86	85
1.00	89	95	95
2.00	88	94	94
4.00	91	96	97
8.00	99	93	92
16.00	98	93	92
Mean L_{eq}	103	101.5	101.3
Mean L_{eq}(A)	100	100	100
s.d.	0.04	0.65	0.77

A. Noise exposures

During the exposures the noise field was monitored with a Larson Davis 814 sound-level meter equipped with a 1/2-in. microphone. The acoustic signal produced by the Electro-Voice Xi-1152/94 speaker system was transduced by a Brüel & Kjær 1/2 inch microphone (model 4134), amplified by a Brüel & Kjær (model 2610) measuring amplifier and fed to a WINDOWS PC-based analysis system. The design and digital generation of the acoustic signal is detailed in Hsueh and Hamernik (1990, 1991).

During exposure, individual chinchillas were confined to cages (10×11×16 in.) with free access to food and water. Peak SPLs of the impact transients in the non-Gaussian conditions were randomly varied between 115 and 129 dB. The impact had a probability of occurring in a 750-ms window of 0.6. The exposure field was uniform to within 2 dB. The four groups of animals were exposed to one of the following exposure protocols:

Group G-5d ($n=16$) Continuous Gaussian noise, 24 h/day for 5 days.
Group G-20d ($n=4$) Interrupted Gaussian noise, 6 h/day for 20 days.
Group NG-5d ($n=12$) Continuous non-Gaussian noise, 24 h/day for 5 days.
Group NG-20d ($n=4$) Interrupted non-Gaussian noise, 6 h/day for 20 days.

Each exposure had in common the same flat spectrum between 0.125 and 10.0 kHz shown in Fig. 1 and was pre-

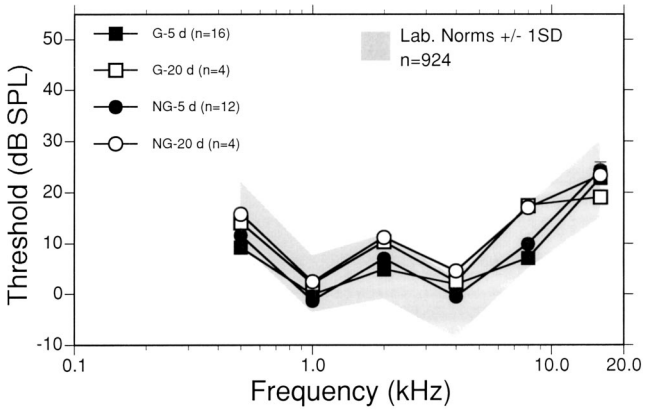

FIG. 3. The group preexposure AEP audiograms for each of the four experimental groups compared to the laboratory norm (shaded area).

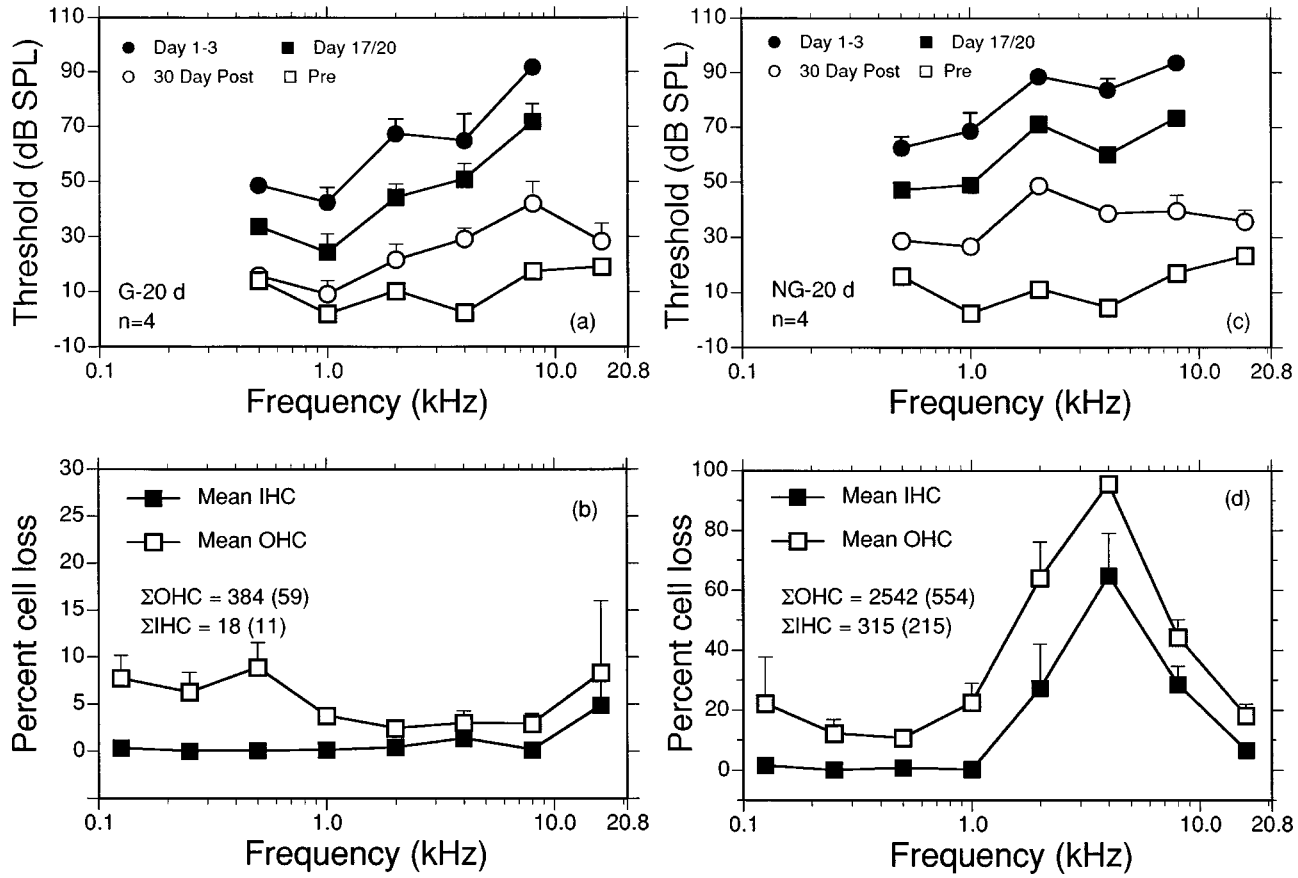

FIG. 4. (a) and (c) Group mean AEP threshold for the animals exposed to the (a) Gaussian noise 6-h/day for 20 days and (c) non-Gaussian noise 6h/day for 20 days. Preexposure threshold (□). 30-day postexposure threshold (○). The maximum threshold measured following exposure on day 1, 2, or 3 (●). The mean threshold measured following exposure on days 17 and 20 (■). (b) and (d) The group mean percent sensory cell loss in adjacent octave band lengths of the basilar membrane for animals exposed to (b) Gaussian noise 6h/day for 20 days and (d) non-Gaussian noise 6h/day for 20 days. Total mean IHC and OHC losses and the standard errors ( ) are indicated.

sented at an Leq-100 dB(A). The exposures differed only in their temporal structure, which was designed to produce two Gaussian and two non-Gaussian exposure conditions. The 5-day continuous exposures produced an asymptotic threshold shift (ATS) while the 20-day interrupted exposures produced a variety of TS patterns during the 20-day course of the exposure which resulted most often in a toughening effect, TS_R. The non-Gaussian conditions were designed in the frequency domain as described by Hsueh and Hamernik (1990, 1991) and were the result of inserting impacts, whose spectra were complementary to the background Gaussian noise, into an otherwise Gaussian signal. The impact peak levels were randomly varied between the limits indicated above and the probability of an impact occurring in a 750-ms window was set at 0.6. The inset in Fig. 1 shows a 15-s sample of the non-Gaussian, nonstationary waveform. Figure 2(a) shows one sample of the noise transients that produced the non-Gaussian signal along with its spectrum. Figure 2(b) shows the spectrum of the Gaussian component of the non-Gaussian signal. Table I presents the octave band levels of each noise exposure. Values shown are the mean values obtained from eight 40-s samples of the digitized waveform.

B. Threshold testing

AEP audiograms were measured at octave intervals from 0.5 to 0.8 or 16.0 kHz. The mean (in dB SPL) of three threshold determinations measured on different days defined each animal's pre- and 30-day postexposure audiogram. For the 20-day interrupted exposures, a complete audiogram (to 8.0 kHz) was measured following days 1, 2, 3, and 17 through 20. Between day 3 and 17 an audiogram was measured every other day. Because of the instability of TS discussed in a later section, the amount of threshold shift recovery (TS_R) at each audiometric test frequency was defined as the difference between the maximum TS measured at that frequency following days 1, 2, or 3 and the mean of the thresholds measured following exposure on days 17 through 20. TS_R is a measure of toughening, i.e., the amount that TS decreases during the 20-day interrupted exposure. A complete audiogram was measured once daily during each of the 5 exposure days of the uninterrupted exposures and the average (in dB SPL) taken over the 5 days established the mean asymptotic threshold levels and shifts.

C. Histology

Following the last AEP test protocol, each animal was euthanized under anesthesia and the right auditory bulla removed and opened to gain access to the cochlea for perfusion. Fixation solution consisting of 2.5% glutaraldehyde in veronal acetate buffer (final pH=7.3) was perfused through the cochlea. After 12 to 24 h of fixation the cochlea was

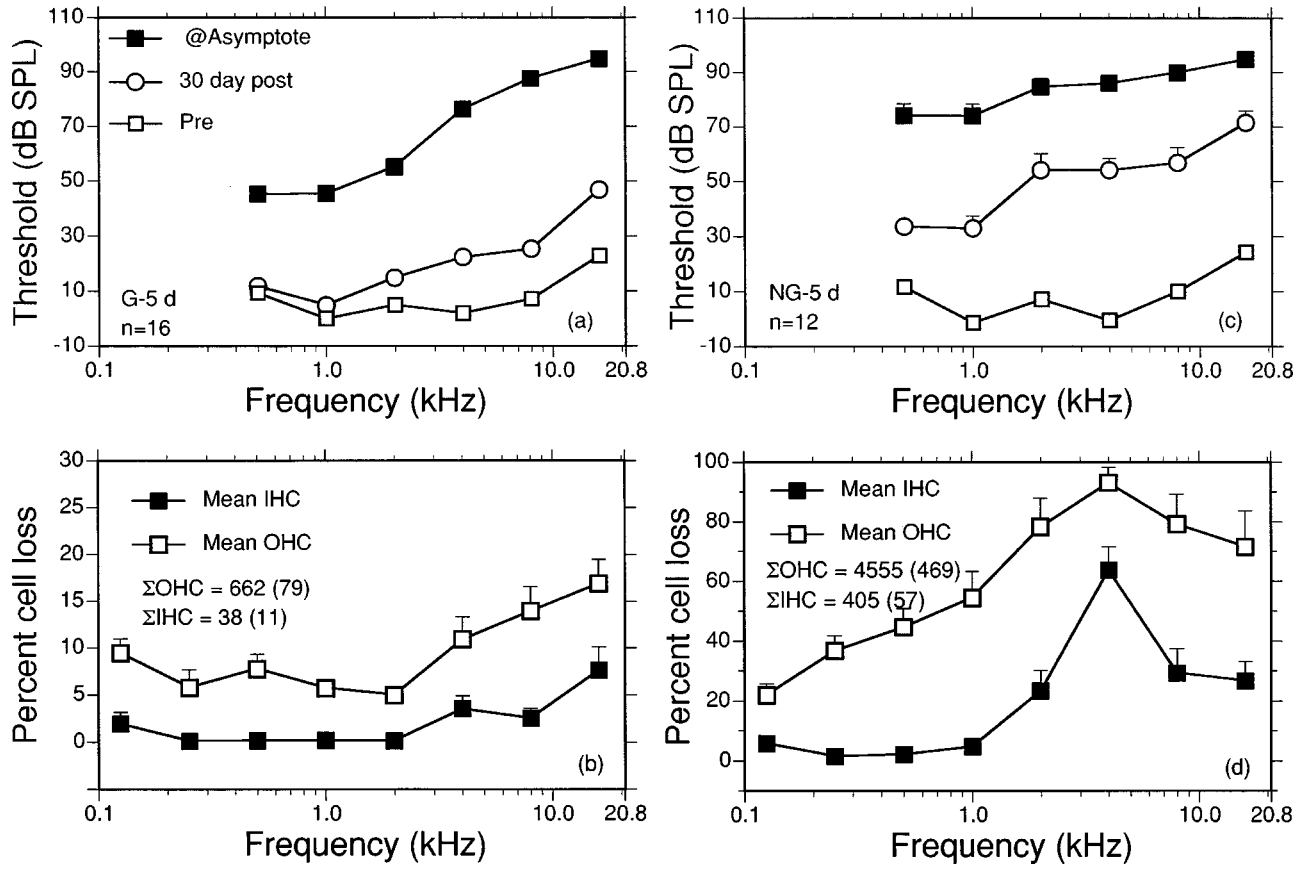

FIG. 5. (a) and (c) Group mean AEP thresholds for the animals exposed to the (a) Gaussian noise 24-h/day for 5 days and (c) non-Gaussian noise 24h/day for 5 days. Preexposure threshold (□). 30-day postexposure threshold (○). Asymptotic threshold levels (■). (b) and (d) The group mean percent sensory cell loss in adjacent octave band lengths of the basilar membrane for animals exposed to (b) Gaussian noise 24-h/day for 5 days and (d) non-Gaussian noise 24-h/day for 5 days. Total mean IHC and OHC loss and the standard errors ( ) are indicated.

postfixed in 1% OsO_4 in veronal acetate buffer. Surface preparation mounts of the entire organ of Corti were prepared and IHC, OHC populations were plotted as a function of frequency and location using the frequency-place map of Eldredge *et al.* (1981). Missing cells were identified by their characteristic phalangeal scars. For purposes of this presentation, sensory cell population data are presented as group averages (in percent missing) taken over octave-band lengths of the cochlea centered on the primary AEP test frequencies.

D. Statistical analysis

The dependent variables reported in this paper are (1) AEP thresholds and threshold shifts, before, during, and following noise exposure(s) and (2) sensory cell losses computed over octave-band lengths and the cochlea. Comparisons of groups of animals receiving different treatments were accomplished by mixed model analyses of variance with repeated measured on at least one factor (frequency). The probability of a type I error was set at 0.05 for all analyses. Statistically significant main effects of frequency are expected in most of the following analyses because of the frequency-specific nature of the chinchilla audiogram (Fay, 1988). For this reason any main effects of frequency will not be repeatedly discussed in the following presentation of results. Analysis of variance summary tables may be obtained from the authors.

III. RESULTS

The initial group mean thresholds for each of the four groups are shown in Fig. 3. In general, the group mean thresholds fall within ± one standard deviation of laboratory norms. Statistical analyses indicates that there was no significant main effect of group, but there was a significant interaction between group and frequency. The shaded region on the AEP audiograms in this figure represents the mean normative AEP audiogram (± one standard deviation) based on a population of 924 chinchillas. The bars on the data points in this and all subsequent figures represent one standard error of the mean. Where no bar is shown the standard error was less than the size of the datum symbol.

AEP thresholds prior to, during, and 30 days after exposure to the Gaussian (G-20 d) and non-Gaussian (NG-20 d) interrupted exposures are shown in Fig. 4 along with the respective group mean cochleograms. Total OHC and IHC losses along with standard errors in parentheses are also given. The ''day 1–3'' data points in Figs. 4(a) and (c) represent the maximum AEP threshold measured following day 1, 2, or 3 of the 20-day interrupted exposures, while the ''day 17/20'' data points represent the mean thresholds measured following exposure on days 17 through 20. In both of these figures the vertical distance between pairs of solid symbols at a given frequency represents the amount of toughening (TS_R) produced by the interrupted exposure at that frequency.

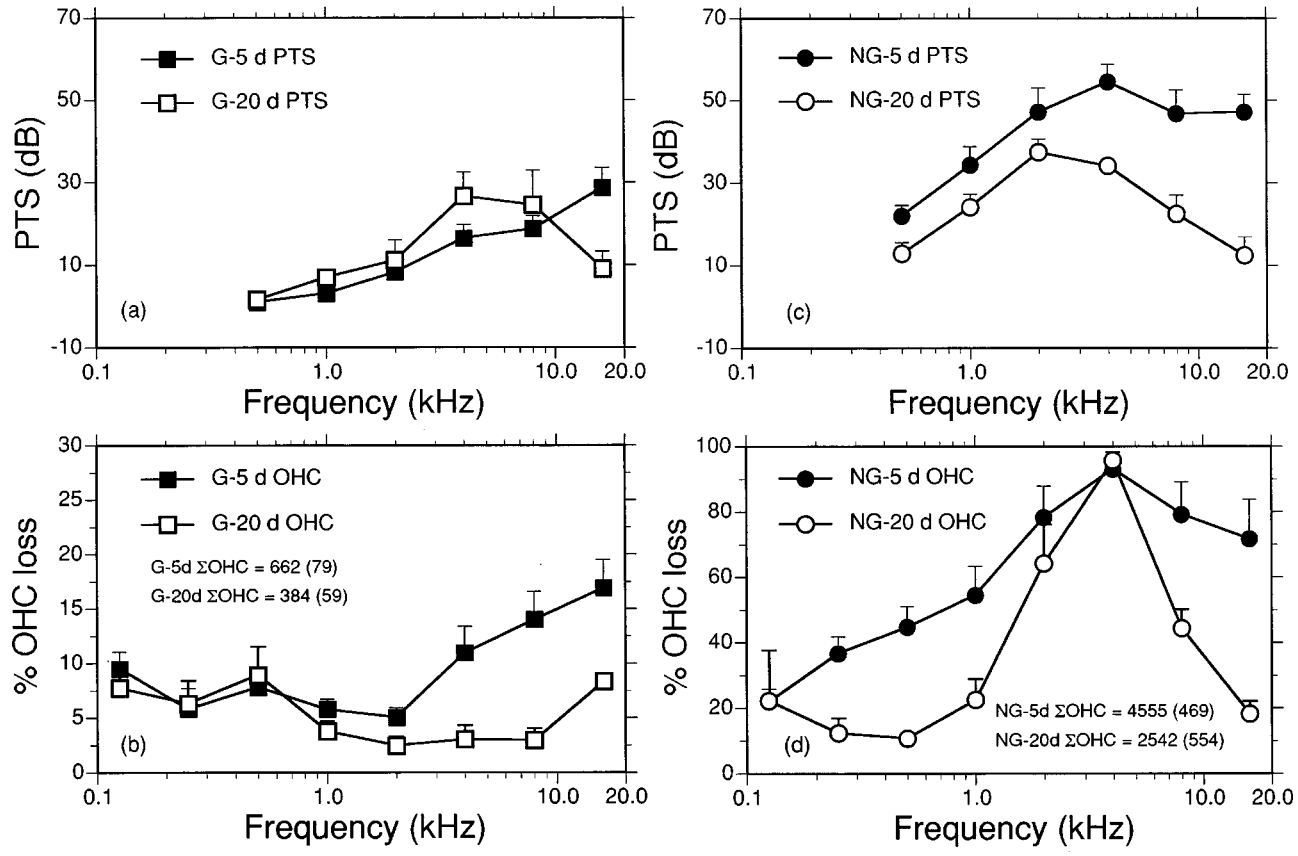

FIG. 6. (a) A comparison of the group mean PTS produced by the Gaussian noise 24-h/day for 5 days (■) and for 6-h/day for 20 days (□). (b) The group mean percent OHC loss in adjacent octave band lengths along the basilar membrane for groups shown in panel (a). (c) A comparison of the group mean PTS produced by the non-Gaussian noise 24-h/day for 5 days (●) and for 6-h/day for 20 days (○). (d) The group mean percent OHC loss in adjacent octave band lengths along the basilar membrane for groups shown in panel (c). Total mean OHC loss for each group and the standard errors ( ) are indicated.

Toughening refers to the improvement in threshold despite the continuing exposure. Note that while the interrupted non-Gaussian exposure produced greater TSs, the amount of TS_R (~15 to 20 dB) in both groups were roughly the same. Permanent effects from these two exposures, as quantified by PTS (the vertical distance between frequency-specific pairs of open symbols) and IHC and OHC loss are also presented.

Figure 5 shows a similar presentation of data from the Gaussian and non-Gaussian continuous 5-day exposures. The solid square symbols in panels (a) and (c) represent the asymptotic threshold levels measured during the continuous 5-day exposures. ATS can be estimated in these two panels by the frequency-specific vertical distance between pairs of square symbols. At and below 4 kHz the ATS produced by the non-Gaussian exposure (60 to 80 dB) was significantly greater than that produced by Gaussian exposure (35 to 80 dB). The lack of a difference above 4 kHz is probably a reflection of the upper limit of our AEP test system. The PTS and sensory cell loss data sets in Figs. 4 and 5 will be compared in the following several figures.

A comparison of the PTS produced by the Gaussian 5 and 20-day exposures and that produced by the two non-Gaussian exposures is shown in Fig. 6 along with the respective group mean OHC losses. The PTS produced by the two Gaussian exposures [panel (a)] varied from 0 to ~30 dB with greater loss at the higher frequencies. There was no statistically significant difference in the PTS produced by the 5- and 20-day Gaussian noise exposures, despite the approximately 15- to 20-dB TS_R (Fig. 4) found in the 20-day group. There was, however, a statistically significant decrease in the total as well as the frequency-specific OHC loss [panel (b)] for the interrupted 20-day exposure. For the two non-Gaussian exposures the interrupted 20-day exposure produced up to 35 dB less PTS than did the energy equivalent 5-day exposure [panel (c)] and a large statistically significant reduction in OHC loss [panel (d)]. PTS varied from 10 to ~35 dB in the non-Gaussian, 20-day interrupted group and from 20 to ~55 dB in the 5-day uninterrupted group. The profile of PTS also differed considerably between the two groups, with much less high frequency loss in the 20-day group. Note that the OHC loss profile generally reflects the PTS profile for each of the four groups shown in Fig. 6.

In Fig. 7 the PTS and OHC loss for the 20-day Gaussian and non-Gaussian exposures are compared in panels (a) and (b). The non-Gaussian exposures produced statistically significant more PTS (up to 26 dB) and OHC loss than did the energy equivalent Gaussian exposure. A similar comparison in panels (c) and (d) between the Gaussian and non-Gaussian 5-day exposures also showed large statistically significant differences in PTS (up to 35 dB) and OHC loss between the two energy equivalent exposures.

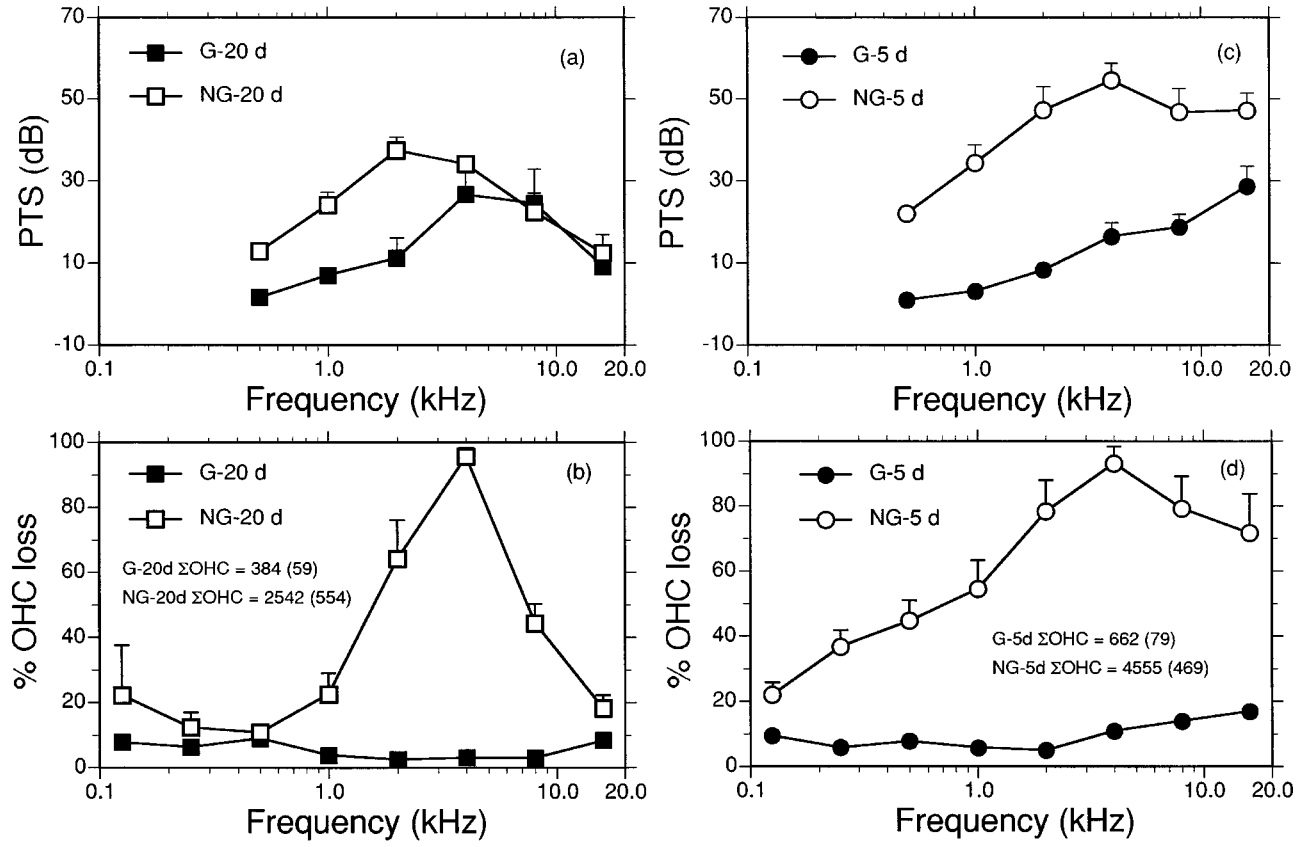

FIG. 7. (a) A comparison of the group mean PTS produced by the Gaussian noise 6-h/day for 20 days (■) and the non-Gaussian noise 6-h/day for 20 days (□). (b) The group mean percent OHC loss in adjacent octave band lengths along the basilar membrane for groups shown in panel (a). (c) A comparison of the group mean PTS produced by the Gaussian noise 24-h/day for 5 days (●) and the non-Gaussian noise 24-h/day for 5 days (○). (d) The group mean percent OHC loss in adjacent octave band lengths along the basilar membrane for groups shown in panel (c). Total mean OHC loss for each group and the standard errors ( ) are indicated.

IV. DISCUSSION

With the exception of the early work of Miller *et al.* (1963), most interrupted exposures have used octave bands of noise to study toughening effects and the potential for protection that toughening may produce for a subsequent exposure. While a number of studies have demonstrated protective effects when the subject is subsequently exposed to a traumatic noise (e.g., Campo *et al.*, 1991; Henselman *et al.*, 1994; McFadden *et al.*, 1997) others have not (Miller *et al.*, 1963; White *et al.*, 1998; Subramaniam *et al.*, 1993). Another protective effect that has received less attention is that produced by the toughening effect on the interrupted noise that produced the toughening. In this situation both the toughening effect and the recovery process that take place during the quiet periods are not easily separated, although the latter influence would be expected to reduce trauma (Ward, 1991). Clark *et al.* (1987) and Bohne *et al.* (1987) showed less PTS and hair cell loss in subjects toughened by an interrupted noise compared to a control group. Ward (1991) also showed that less trauma is produced by interrupted/intermittent exposures compared to equivalent energy controls. His experimental paradigm did not allow for any estimate of TS_R. Hamernik and Ahroon (1998) used high-level narrow-band impacts and a large sample size to study the toughening phenomena. The impacts clearly produced a TS_R. They showed, however, that the toughened subjects had approximately the same levels of PTS and sensory cell loss as control subjects exposed to the same impacts but on an uninterrupted schedule. In our present study, Fig. 4 shows that both Gaussian and non-Gaussian exposures, having the same energy and spectra, produce a clear 15- to 20-dB TS_R across the entire range of test frequencies (0.5 through 8.0 kHz). The threshold shifts, however, for the non-Gaussian exposure were greater. And, in agreement with the above studies that showed a reduction in trauma, both of the interrupted exposures showed reduced sensory cell loss. For the non-Gaussian interrupted exposure [NG-20 d] there was also a large (up to 35 dB) reduction in PTS [Fig. 6(c)] when compared with the uninterrupted exposure.

While the toughening effect is similar for both the Gaussian and non-Gaussian exposures, the level of trauma produced by both the interrupted and uninterrupted non-Gaussian exposures exceeds by a large amount (Fig. 7) the trauma produced by the respective Gaussian exposures. This increased trauma from the non-Gaussian exposures agrees with our earlier data (Lei *et al.*, 1994; Hamernik and Qiu, 2001). The large differences in PTS and sensory cell loss between the effects of Gaussian and non-Gaussian exposures are likely related to the excessive stress/strain on the epithelial tight cell junctions induced by the high-level impulsive forces and the subsequent momentum changes that are produced. Disrupting the integrity of the tight cell junctions with

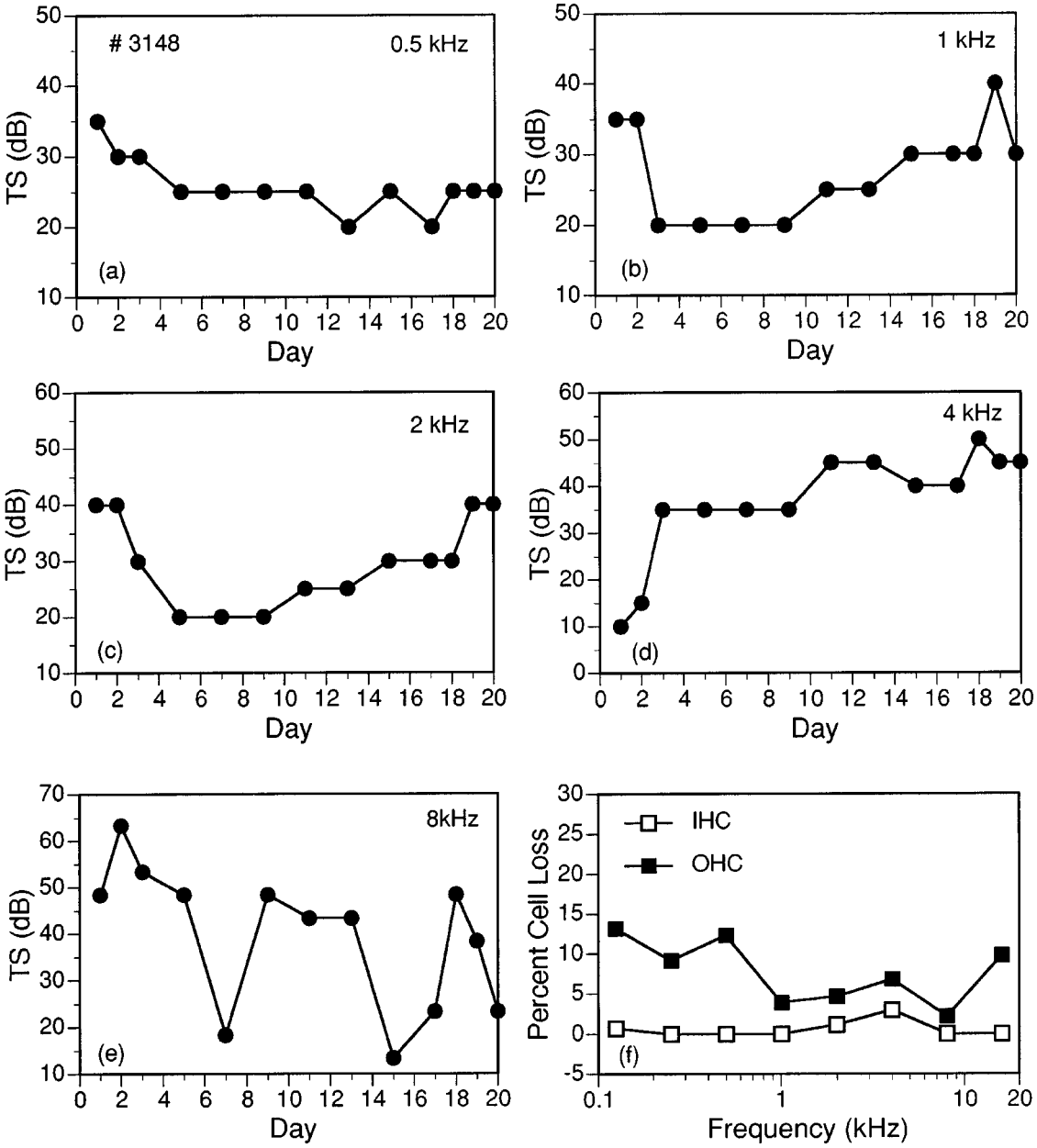

FIG. 8. Examples of an individual animal's TSs, measured at the indicated AEP test frequency [panels (a)–(e)], during the course of the 20-day exposure. The animal is #3148 from group G-20 d. The octave band percent IHC and OHC loss is shown in panel (f).

the entry to endolymph into the space below the reticular lamina is known to increase the extent of cell loss (Bohne and Rabbitt, 1983). Also, the severe tearing of the organ of Corti seen with high-level impacts (Hamernik *et al.*, 1984) probably releases a variety of free radicals into the sensory cell environment as a consequence of the processes involved in clearing the cellular debris. These highly reactive species are also known to have a detrimental effect on cochlear function (Jacono *et al.*, 1998). In addition, the induction of apoptosis may further exacerbate these effects (Hu *et al.*, 2002).

For both non-Gaussian exposures $\beta=33$ (approximately). This is an average value calculated from eight 40-s samples of the temporal waveform. The above results would not be anticipated from an application of the equal energy hypothesis, which is the basis of the current international noise standard for the protection of hearing. These results also show that the temporal structure, whether altered through intermittence or through a non-Gaussian peak distribution, can exert a strong effect on the outcome of an exposure. Much of the variability seen in the human demographic data (Mills *et al.*, 1996) may be the result of a neglect of temporal variables. The temporal variables of an exposure need to be taken into account in the formulation of damage risk criteria for noise exposure.

While most animals in the two interrupted exposure paradigms showed a TS_R at most frequencies, there were some frequencies that displayed ''nontypical'' TS configurations over the course of the exposure. One animal in particular was quite variable and showed an interesting assortment of TS functions, any one of which could be found in the other subjects at some frequency. Figure 8 shows the TS measured in this animal (#3148) during the course of the

Gaussian, 20-day exposure along with the animal's cochleogram [panel (f)]. At 0.5 kHz TS follows a pattern typical of the toughening phenomena. The animal shows a 35-dB TS following the first day of the exposure. Over the next several days TS decreases and reaches a stable value of about 25 dB, i.e., a $TS_R = 10$ dB. At 1.0 and 2.0 kHz the TS pattern is ''U'' shaped, with TS initially decreasing as much as 20 dB followed by a gradual increase to levels close to or approaching those measured following the first day's exposure. There is little or no TS_R at these frequencies. At 4.0 kHz TS is initially relatively low (~10 dB) but then increases over the course of the exposure to ~40 to 45 dB. At this frequency the cochlea has become more susceptible to the noise as the exposure continued, i.e., a $-TS_R$. Finally, at 8.0 kHz TS measures are unstable. TS fluctuates as much as 30 dB over the course of the exposure. The large TS fluctuations seen in the ''unstable'' configuration could be found at various frequencies and on different exposure days in different animals. The AEP waveforms recorded prior to a fluctuation, on the day of the TS dip and on the day following the dip, showed clear and regular intensity-dependent AEP waveforms with threshold well delineated. Clearly, a variety of different processes both protective and pathological must underlie these functions which eventually resolve and yield stable but shifted hearing thresholds for the subject.

V. ANIMAL USE

The care and use of the animals used in this study was approved by the Plattsburgh State University of New York Institutional Animal care and Use Committee. In conducting this research the investigators adhered to the Guide for Care and Use of Laboratory Animals, as promulgated by the Committee on Care and Use of Laboratory Animals in the Institute of Laboratory Resources Commission on Life Sciences, National Academy of Sciences-National Research Council, revised 1985.

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