Noise Priming and the Effects of Different Cochlear Centrifugal Pathways on Loud-Sound-Induced Hearing Loss

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Rajan, R. Noise priming and the effects of different cochlear centrifugal pathways on loud-sound-induced hearing loss. J Neurophysiol 86: 1277–1288, 2001. Priming/conditioning the cochlea with moderately loud sound can reduce damage caused by subsequent loud sound. This study examined immediate effects of short-term priming with monaural broadband noise on temporary threshold shifts (TTSs) in hearing caused by a subsequent loud high-frequency tone and the role of centrifugal olivocochlear pathways. Priming caused delay-dependent changes in tone-induced TTSs, particularly or only at frequencies higher than the peak tone-affected frequency, through two general effects: a short-lasting increase in cochlear susceptibility to loud sound and longer-lasting complex end effects of centrifugal pathways. The results indicated the following points. Priming noise had “pure” cochlear effects, outlasting its presentation and declining with delay, that exacerbated tone-induced TTSs at frequencies higher than the peak tone-affected frequency. The centrifugal uncrossed medial olivocochlear system (UMOCS) could prevent this noise exacerbation and as this noise effect declined, could even reduce tone-induced TTSs below those to the unprimed tone. For longer delays, when priming noise no longer had any exabrative “pure” cochlear effects on TTSs, UMOCS exacerbated TTSs above those to the unprimed tone. The crossed medial olivocochlear system (CMOCS) appeared to show a gradual “build-up” of effects postpriming. A parallel study showed it exercised no end effect on TTSs when noise and tone were concurrent. With priming, CMOCS effects were observed. For the shortest priming delay, the CMOCS blocked a UMOCS effect preventing noise exacerbation of tone-induced TTSs. For longer delays, CMOCS end effects, when present, reduced tone-induced TTSs below those to the unprimed tone. The CMOCS may oscillate between producing these effects and exerting no end-effect. With increasing delay CMOCS protection occurred in a greater proportion of animals. Finally, with a delay of 600 s between primer and loud tone, all these systems appeared to have reset to normal so that TTSs were similar to those in the unprimed condition. Thus the effects of short-term priming are not simple and do not suggest that centrifugal pathways act automatically as a protective system during such priming.

INTRODUCTION

Two protocols termed “conditioning” or “toughening” reduce loud-sound-induced cochlear damage. In the protocol of relevance here, an initial moderately loud sound can reduce the damage caused by later loud sounds (e.g., Campo et al. 1991; Canlon et al. 1988; Fiorino et al. 1989; Kujawa and Liberman 1997; Miyakita et al. 1992; Rajan 1996a; Rajan and Johnstone 1983; Ryan et al. 1994; Zheng et al. 1997b). Here a moderate-level “conditioning” sound, causing little or no damage, is presented followed by a short rest period and then exposure to short-duration trauma. In an early study (Rajan 1996b; Rajan and Johnstone 1983), the conditioner was a short-duration tone causing some temporary loss in cochlear threshold sensitivity (temporary threshold shifts, TTSs). After complete recovery over 30 min, a higher-level same-tone exposure, also causing TTSs, was the terminal trauma. Subsequent studies (summarized by Canlon 1996; Subramaniam et al. 1996) examined conditioning effects on permanent threshold shifts (PTSs) and/or morphological damage to cochlear structures caused by short-duration high-intensity sound, generally with the same spectrum as conditioner, given after the rest period. In both variants of this protocol, conditioned animals show less damage (TTSs, PTSs, or morphological damage) to terminal trauma compared with unconditioned animals.

Conditioning effects may (Fiorino et al. 1989; Kujawa and Liberman 1997; Zheng et al. 1997a,b) involve centrifugal olivocochlear pathways that, in other conditions, reduce loud-sound-induced TTSs (Cody and Johnstone 1982; Rajan 1992, 1995a,b, 1996a, 2000; Rajan and Johnstone 1983, 1988; Reiter and Liberman 1995) or PTSs (Handrock and Zeisberg 1982; Liberman and Gao 1995; Zheng et al. 1997a). A recent study (Rajan 2000) showed that the crossed medial olivocochlear system (CMOCS) acted only when a loud tone was presented binaurally (as shown previously for this pathway) and uncrossed pathways [likely uncrossed MOCS (UMOCS), not lateral olivocochlear system (LOCS)] (see Rajan 2000) acted when a loud tone was presented either monaurally or binaurally with concurrent noise. The nontraumatic noise itself (in the absence of UMOCS) exacerbated the tone-induced TTSs. The present study was designed to examine the time course of this effect and the role of centrifugal pathways in a protocol with relevance to conditioning/toughening. The term “priming” is used to describe the protocol because here effects of the preceding nontraumatic stimulus on cochlear damage to subsequent terminal trauma were remarkably different to studies where conditioning stereotypically reduces damage induced by terminal trauma.

METHODS

Animal treatment and measurement of hearing sensitivity

Procedures for animal treatment and measuring cochlear sensitivity have been detailed before (Rajan 1995a; Rajan et al. 1991). In brief,
adult cats weighing between 3 and 6 kg were tested under procedures approved by the Monash University Standing Committee on Ethics in Animal Experimentation and conforming to guidelines of the National Health and Medical Research Council of Australia. Cats were anesthetized (60 mg/kg) and maintained with continuous intravenous infusion of pentobarbital sodium (Nembutal) at 2–3 mg • kg⁻¹ • h⁻¹. Depth of anesthesia was monitored through continuous recording of rectal temperature, electrocardiograms (ECG), electromyographic (EMG) activity from forearm muscles, and regular hourly checks of response to strong noxious pinching of the forepaw, the presence of pupillary dilatation, and absence of corneal reflexes. Output from ECG/EMG electrodes was displayed on an oscilloscope and fed into a speaker for continuous monitoring of the cat’s condition and depth of anesthesia. Body temperature was maintained at 37.5 ± 0.5°C (range) by a thermostatically controlled warming blanket, regulated by feedback from a rectal probe. Cats were tracheostomized and artificially ventilated on room air. Tidal volume was determined from normogram data and rate set between 20 and 25 breaths/min depending on the cat’s weight.

Stainless steel electrodes were implanted against the round window membrane of both cochleas to measure cochlear hearing sensitivity (Rajan et al. 1991). Hearing sensitivity was assessed by measuring thresholds for the compound action potential (CAP) of the auditory nerve at frequencies from 1 to 40 kHz that were then compared with normative data (Rajan 1995a; Rajan et al. 1991), and only animals with normal hearing sensitivity bilaterally from 1 to 40 kHz were used.

Tones and noise stimuli to each ear were generated independently by one of four channels of a digital synthesis system, gated under computer control, and passed through separate computer-controlled attenuators before feeding into one of four channels of an electronic mixer box. The mixer was used to manually switch delivery of stimuli to each ear as desired. Cross talk between different channels of the mixer was more than −100 dB up to 10 kHz, −100 dB from 10 to 20 kHz, declining to −95 dB at 40 kHz. Two output channels from the mixer box separately fed sound to one of two Sennheiser HD 535 speakers, each in housing leading to a sound delivery tube in one external auditory meatus (Rajan et al. 1991).

Surgical inactivation of efferent pathways

Inactivation of components of cochlear efferent pathways was made using surgical lesions at the floor of the fourth ventricle after removing overlying cerebellum (Rajan 1995a). Lesions were made after measuring the CAP audiogram and prior to any priming or trauma (see following text) and were made to totally de-efferent the test cochlea or lesion only crossed efferent pathways (bilaterally), leaving uncrossed pathways intact (see Rajan 1995a for locations of cuts). To totally de-efferent a cochlea, a lesion was made 1.5–2 mm lateral of the midline and on the side ipsilateral to the test cochlea. To cut only crossed pathways (bilaterally), the lesion was made exactly at the midline. Lesions were 6–8 mm long, extending about the full length of the colliculi, identifiable on the ventricular floor. Postmortem histology, occasionally combined with staining for acetycholine esterase (which stains efferent pathways), was used to confirm the location of cuts (Rajan 1995a; Warren and Liberman 1989).

In all animals with brain-stem lesions, the CAP audiogram was measured prior to and after placing any lesions. Heart rate, ECG waveform, and body temperature were also noted prior to lesion and re-checked immediately postlesion.

Traumatic loud-sound exposures and measurement of cochlear desensitization

In all experiments, testing (both priming and loud sound exposure) was monaural to the one ear. The primer was broadband noise (0.5–40 kHz), presented at 80 dB SPL continuously for 15 min, monaurally to the test ear that would subsequently be exposed to the standard traumatic tone. Delays between the end of noise primer and traumatic tone were 5, 80, 200, 300, 400, or 600 s. In animals with delay ≥200 s, CAP thresholds from 9 to 28 kHz (see following text) were often re-measured in the interval between primer and loud tone, generally starting 10 s postprimer.

The traumatic tone to cause TTSs was at 13 kHz and was presented at 100 dB SPL continuously for 15 min. This was the same trauma used in a concurrent study (Rajan 2000) of effects of concurrent noise on TTSs to the traumatic tone, and the role of cochlear efferents in such a context. As noted there, this frequency is from within the most sensitive part of the cat CAP audiogram (Rajan et al. 1991); frequencies from this region cause TTSs more easily than do other frequencies and more readily activate protective effects of the crossed efferent pathway (Rajan 1995b). For any delay, ears from different animals were grouped according to the status of the efferent pathways to that ear: all efferent pathways intact (OC+), all pathways cut (OC−), or only crossed pathways cut (COC−).

After loud-tone exposure, CAP thresholds were measured 5 min after the end of the loud tone at frequencies from 7 to 30 kHz, in constant (but not linear) order. It took ~2.5 min to measure thresholds from 9 to 28 kHz bilaterally. Frequency-specific TTSs were calculated as the difference between pre- and postloud tone thresholds. Comparisons between groups were comparisons between TTSs at corresponding frequencies. Two-way repeated-measures ANOVAs were used to compare effects between different experimental conditions. If the ANOVA revealed a significant difference between conditions, generally with a significant interaction term between experimental condition and frequency, unpaired Student’s t-tests were used to compare threshold losses at corresponding frequencies in the two conditions.

Finally, under the anesthetic conditions of this study, middle ear muscles are not active to loud sound, as demonstrated in Rajan (1995a) using identical anesthetic conditions and similar loud sounds, and would not be involved in effects described here.

RESULTS

Basic effects of olivocochlear pathways on TTSs induced by a loud tone in a background of silence or of concurrent noise

The effect of noise primer on TTSs caused by the subsequent loud tone will be contrasted against TTSs caused by the unprimed tone alone and TTSs when noise and tone were concurrent. The latter two effects were examined in a parallel study (Rajan 2000), but as they are germane here, are briefly summarized here and in Fig. 1.

In totally de-efferent (OC−) ears (group Noise 7 OC− ears of Rajan 2000) monaural 80 dB SPL noise concurrent with the loud tone resulted in larger TTSs at all frequencies (Fig. 1A) than in OC+ tone-alone ears (group Silence 1 of Rajan 2000). When cochlear efferents were intact (Rajan 2000: group Noise 6 OC+ ears) (Fig. 1A), this noise effect was absent and TTSs were similar (Fig. 1A) to TTSs in tone-alone OC+ ears of group Silence 1. (The previous report also showed noise itself did not cause TTSs but exacerbated tone-induced TTSs in OC− ears.) This monaural protection, from exacerbative effects of concurrent noise, was due to uncrossed OC (UOC) pathways. When only the COC pathway was lesioned (group Noise 7 COC−, Rajan 2000), TTSs to tone in noise were still similar to TTSs to tone in noise in OC+ ears of Noise 6 (and tone-alone ears of Silence 1). Thus under monaural conditions,
With this background, the effects of this study, in which the noise was presented prior to loud tone, are described.

**Priming with nondamaging noise results in complex effects on TTSs to a subsequent loud sound**

The effects of noise primer on TTSs to a subsequent loud tone in all-efferent-intact (OC+) ears are shown in Fig. 2 and compared with TTSs in OC+ unprimed ears exposed only to the monaural loud tone (“tone-only”) group. Comparisons were made using two-way repeated-measures ANOVAs, with post hoc unpaired Student’s t-tests on TTSs at corresponding frequencies between a primed group versus (unprimed) tone-only group when the ANOVA revealed a significant condition difference, or a significant condition \( \times \) frequency interaction. [In all groups, TTSs varied with frequency in the manner shown in Fig. 1 and ANOVA F for Frequency was always significant (\( P < 0.001 \)) and is not reported. For t-tests, because of the number of groups and frequencies, \( P \) values for significant differences are not detailed. Significance was taken as \( P < 0.05. \)]

In essence, compared with unprimed (“tone-only”) ears, priming in OC+ ears increased or reduced TTSs to the subsequent loud tone as a complex function of delay between primer and tone. Generally, TTS exacerbation (by >4 dB) was at >15 kHz, with peak exacerbation just >10 dB from \( \approx 17–22 \) kHz. TTS reductions (by >4 dB) tended to extend across the affected range, generally peaking at >15 kHz.

For priming delays \( \leq \)200 s (Fig. 2, A–C), TTSs in primed OC+ groups “switched” at different delays between reductions or exacerbations in TTSs compared with the unprimed tone-alone group. With 5-s delay (\( n = 5 \)), TTSs at >12–22 kHz (i.e., at most tone-affected frequencies) were significantly greater than in the tone-only OC+ group (ANOVA: \( P = 0.014 \) for condition F, \( P = 0.001 \) for interaction F), with peak difference of >10 dB in the range from 16 to 22 kHz (Fig. 2A2). This reversed with 80-s delay (\( n = 5 \); Fig. 2B) when TTSs at most tone-affected frequencies (13–28 kHz) were lower than in the tone-only group (\( P < 0.005 \) for condition and interaction factors; Fig. 2B2). These lower TTSs were comparable (\( P > 0.35 \) for condition and interaction factors) to TTSs in OC+ ears with binaural unprimed tone-alone exposure (see Fig. 1B). As noted in the preceding text, in the latter condition, the OC pathway acts (alone) to protect the cochlea (Rajan 2000). With 200-s priming delay (\( n = 5 \); Fig. 2C), TTSs from 15 to 24 kHz (i.e., from the peak tone-affected frequency to higher frequencies) were now again greater than in the unprimed (monaural) tone-only group (condition \( P = 0.022 \), interaction \( P < 0.001 \)) with peak exacerbation of >12 dB at 20 kHz (Fig. 2C2). These “oscillations” in TTS in primed OC+ ears compared with unprimed tone-only ears are seen clearly in difference curves (Fig. 2, A2–C2).

For longer delays of 300 and 400 s (Fig. 2, D and E), a dichotomy of effects occurred: some animals showed increased TTS and others decreased TTSs compared with the unprimed tone-only group. With 300-s delay (Fig. 2D) in most animals (5/6), TTSs at 16–24 kHz (high-frequency slope of affected range) were significantly greater (condition and interaction factors, \( P < 0.005 \)) with peak exacerbation of >12 dB at \( \approx 18–20 \) kHz (Fig. 2D2). In one animal, TTSs at almost all frequencies were markedly lower (Fig. 2D2) than in the mon-
aural tone-only group and comparable to low TTSs with unprimed binaural tone exposure (cf. Fig. 1B). This dichotomy was more pronounced with 400-s delay ($n = 7$; Fig. 2E). In four animals TTSs at 16–24 kHz (same frequencies as at 300-s delay) were increased compared with the tone-only group (condition $P = 0.052$, interaction $P < 0.001$), with peak exacerbation of $\sim12$ dB at 18–22 kHz (Fig. 2E2). In the other three animals, TTSs at most frequencies (13–28 kHz) were markedly lower than in the unprimed tone-only group ($P < 0.001$ for condition and interaction factors; Fig. 2E2) and similar to low TTSs with binaural unprimed tone-only exposure.

Finally, with 600-s delay between primer and tone ($n = 6$; Fig. 2F), TTSs were similar to the tone-only group ($P > 0.05$ for condition and interaction factors) with differences generally $<3$ dB (Fig. 2F2). Thus 10 min after the 15-min-long primer, the primer did not modulate TTSs to the tone.

These complex sequelae of priming consisted of two effects. First, the noise primer had “pure” cochlear-only effects that exacerbated tone-induced TTSs well post primer, with this effect decaying rapidly postprimer. Second, COC and UOC end effects were complex such that TTSs to the tone could be reduced (protected) or increased (exacerbated) from TTSs caused by an unprimed tone-alone exposure. These two general effects are distinguished and treated separately in the following text.

Nondamaging priming noise has lasting effects that exacerbate TTSs to subsequent loud sound

Noise itself could exacerbate TTSs, as established in ears where the cochlea was totally de-efferented (OC−) prior to testing to remove any OC effects. “Raw” TTSs from OC− groups at different delays are shown in Fig. 3, A–D, and E

FIG. 2. Effects of a priming broadband noise on TTSs to a subsequent loud tone vary as a function of the delay between primer and tone. The primer was broadband noise at 80 dB SPL, the loud tone was at 13 kHz at 100 dB SPL, and both were delivered monaurally to the same ear for 15 min. Each panel presents data from a test group with delay between primer and loud tone (delay indicated below panel label). A1–F1: TTSs in primed efferent-intact (OC+) ears (●, ●) compared with TTSs in control OC+ ears exposed only to loud tone with no priming (○). Data are mean data (error bars, SE). D1 and E1: 2 data sets for primed ears. For these delays data from primed ears fell into 1 of 2 categories: cases where TTSs were exacerbated (○) from those due to the unprimed tone-only exposure and cases where TTSs were reduced (●) from those due to the unprimed tone-only exposure. A2–F2: difference between the mean frequency-specific TTSs in primed ears and in (control) unprimed tone-only ears in the panel directly above. In D2 and E2, 2 difference curves are shown for the difference between the primed “exacerbated-TTS” and “reduced-TTS” subgroups at that priming delay and control ears. 0, the range $\pm 4$ dB around 0 dB difference; generally differences $<4$ dB were not statistically significant.
shows differences in TTSs in each group and the unprimed tone-only group. The latter panel also shows the exacerbative effect of this noise on the same loud tone when both were concurrent (Noise 7 OC– of Rajan 2000). Compared to the tone-only group, in the concurrent-noise group TTSs were increased mainly >15 kHz, the peak tone-affected frequency, but small increases also occurred <15 kHz. With 5-s priming delay (n = 5), only TTSs from 15 to 24 kHz were significantly exacerbated compared with the tone-only group (P < 0.001 for condition and interaction factors). The effects diminished markedly with 80-s delay (n = 5) and only 15–17 kHz suffered significantly higher TTSs compared with the tone-only group (condition P = 0.12, interaction P = 0.018). Finally, with delay ≥200 s, noise did not exacerbate tone-induced TTSs (200 s, n = 5; 400 s, n = 4; 600 s, n = 5) which, in all three groups, were similar to the tone-only group.

Pair-wise comparison between groups where noise was coupled with loud tone showed the progressive decrease with delay in noise exacerbation of TTSs. Thus 5-s priming delay resulted in TTSs at 11–13 and 19–28 kHz being significantly lower (P < 0.005 for condition and interaction factors) than in the concurrent noise group and only 14- to 18-kHz TTSs were similar. With 80-s delay, 18–24 kHz suffered significantly lower TTSs (condition P = 0.14, but interaction P = 0.001) than with 5-s delay. Since noise exacerbated TTSs from 15 to 24 kHz in the latter group compared with the tone-only group, then by 80 s all these frequencies, other than 15–17 kHz, had recovered from noise exacerbation. By 200-s delay, there was no noise exacerbation: comparison against the primed 80-s delay group showed significantly lower TTSs from 11 to 19 kHz with the longer delay (condition P = 0.027, interaction P = 0.024). Finally, pair-wise comparison of OC− groups primed with delays of 200, 400, or 600 s showed no significant differences (see Fig. 3, C–E).

Noise priming results in complex TTS end-effects of uncrossed and crossed efferent pathways

Comparison of OC+ and OC− primed ears suggested priming also resulted in complex end effects of OC pathways on tone-induced TTSs. For example, with 80-s priming delay, cochlear efferents appear to mitigate noise exacerbative effects and further protect the cochlea: TTSs in OC− primed ears were generally similar to unprimed tone-only (OC+) ears (except at 15–17 kHz), but TTSs from 13 to 28 kHz in OC+ primed ears were lower than in the unprimed tone-only group. In contrast, with 200-s delay, cochlear efferents exacerbated TTSs: TTSs at 15–24 kHz in OC+ primed ears were greater than in the unprimed tone-only group but in OC− primed ears, similar to TTSs in the unprimed tone-only group. Most dramatically, with 400-s delay, TTSs in OC− primed ears were similar to the unprimed tone-only group, but TTSs in OC+ primed ears could be exacerbated or reduced from the control group.

To examine these effects, selective lesions of the COC pathway while leaving intact UOC pathways were used (noting the converse is not possible). Comparison of such COC− ears against the unprimed tone-only group and against OC+ and OC− groups at the same delay allowed inferences about the role of COC and UOC pathways. Effects varied with delay and appeared, at the first level, to correlate with the presence of noise exacerbation of tone-induced TTSs.

SHORT DELAYS WITH NOISE-INDUCED TTS EXACERBATION: UOC ACTION CAN PREVENT THE NOISE EFFECT. As shown previously, with 5-s priming delay noise exacerbated tone-induced TTSs in OC− ears (Fig. 3E) and OC+ ears (Fig. 2A) to similar levels above the unprimed tone-only group (OC+ vs. OC− groups; condition P = 0.93, interaction P = 0.38), suggesting OC pathways would not modulate noise exacerbation of TTSs. Selective COC pathway de-efferentation (n = 5) showed a
surprising result. TTSs in COC− ears were similar (Fig. 4A1) to the unprimed tone-only group (condition $P = 0.096$, interaction $P = 0.65$) but significantly lower across most of the range than in primed de-efferented (OC−; Fig. 4A2; condition and interaction $P < 0.001$; significant at 14–26 kHz) or efferent-intact (OC+; Fig. 4A3; condition $P = 0.007$, interaction $P = 0.024$; significant at 12–22 kHz) ears. Thus UOC pathways could prevent noise exacerbation of TTSs but only in the absence of the COC pathway.

The effect of different OC components was calculated (Fig. 5) from differences between TTSs in OC+ and OC− ears (to index the effect of having all OC pathways intact; “All-OC” effects, line in Fig. 5), COC− and OC− ears (“UOC-alone” effect; open symbols), and COC− and OC+ ears (“COC-alone” effect; closed symbols). With 5-s priming delay (Fig. 5A), UOC pathways reduced TTSs across the affected frequency range not just frequencies at which noise exacerbated TTSs. The apparent frequency-specific increase in TTSs caused by the COC pathway reflects that in OC+ ears this pathway blocked UOC effects, and not necessarily that it exacerbated TTSs (see DISCUSSION).

The ability of UOC pathways to prevent noise exacerbation was also present with the next shortest delay, 80 s. Here, in OC+ ears (Fig. 2B), OC pathways prevent the slight noise exacerbation of TTSs (Fig. 3E) and, more, reduce monaural tone-induced TTSs to levels (cf. Fig. 1) seen with COC protection in binaural tone-alone exposure. Hence, OC− primed ears suffered significantly higher TTSs at most frequencies (12–28 kHz) than OC+ primed ears (condition and interaction $P < 0.001$). The total protection in OC+ ears was due to both OC pathways. Lesioning the COC pathway (COC−; $n = 5$) resulted in TTSs consistently lower than in OC− ears (Fig. 4B2; condition $P = 0.013$ with interaction $P = 0.095$; significant differences at 12–24 kHz) and in the tone-only group (Fig. 4B1; Condition $P = 0.024$, Interaction $P = 0.7$; but significant differences only at 13–15 and 24–28 kHz). Thus UOC pathways contributed to overall TTS reductions in OC+ primed ears. However, TTSs in COC− ears were generally larger than in OC+ ears (Fig. 4B3; condition $P = 0.07$ but
reducing TTSs below those in the unprimed tone-only group. Reductions, preventing the slight noise exacerbation and further at 15 and 16 kHz. Thus both OC pathways contributed to TTS protective COC pathway effect to reduce TTSs below those in and, additionally, exercise a protective effect that works with a reductions: UOC pathways prevent noise exacerbation of TTSs 80-s delay, both UOC and COC pathways contribute to TTS TTSs) appears suppressed/blocked by the COC pathway. For (which prevent noise exacerbation without further reducing 11 dB from 17 to 20 kHz.

In summary, for short priming delays at which noise exacerbates tone-induced TTSs, UOC pathways can prevent this effect. At the shortest delay (5 s), this effect of UOC pathways which prevent noise exacerbation without further reducing TTSs) appears suppressed/blockaded by the COC pathway. For 80-s delay, both UOC and COC pathways contribute to TTS reductions: UOC pathways prevent noise exacerbation of TTSs and, additionally, exercise a protective effect that works with a protective COC pathway effect to reduce TTSs below those in the unprimed tone-only group.

LONGER DELAYS WITH NO NOISE-ALONE EFFECT: UOC ACTION EXACERBATES TTSs AND COC ACTION CAN REDUCE TTSs. Selective de-efferentation showed that for longer priming delays of 200 and 400 s, when noise exacerbation of tone-induced TTSs was absent, UOC pathways exacerbate tone-induced TTSs and COC pathways can reduce TTSs.

With 200-s delay, OC pathways significantly exacerbate TTSs at frequencies from the peak-affected frequency to most high frequencies: in OC+ primed ears TTSs from 15 to 24 kHz were higher than in the tone-only group (Fig. 2C) and the OC− primed group (condition \( P = 0.007 \), interaction \( P < 0.001 \)). Lesioning the COC pathway showed UOC pathways were responsible for this exacerbation. TTSs at high frequencies in COC− primed ears (\( n = 5 \)) were significantly higher than in the tone-only group (Fig. 4C1; condition and interaction \( P < 0.001 \); significant differences at 15−22 kHz) and the OC− primed group (Fig. 4C2; condition and interaction \( P < 0.001 \); significant differences at 14−24 kHz), but were similar to TTSs in OC+ primed ears (Fig. 4C3; condition \( P = 0.44 \), interaction \( P = 0.95 \)). The difference curves (Fig. 5C) confirmed the conclusions from the raw data. UOC pathways were responsible for all TTS exacerbations and there was no COC pathway modulation of TTSs. TTS exacerbation by >5 dB were found from 14 to 24 kHz, with peak exacerbation of ~13 dB at 19 kHz.

With 400-s delay, in OC+ ears TTSs could be increased (4/7 animals, Fig. 2E) from TTSs in the monaural tone-only group or decreased (3/7) and comparable to the COC-protected TTSs with binaural tone-only exposure (Rajan 2000). In the OC− primed group, TTSs were uniformly lower than in the protected OC+ subgroup (condition and interaction factors both \( P < 0.005 \)) but, at 17−24 kHz, were greater than in the exacerbated OC + subgroup (condition \( P = 0.1 \), interaction \( P < 0.001 \)). Since TTSs in the OC− and tone-alone groups were similar, these comparisons of the OC− group against each OC+ sub-group suggest TTS exacerbation or reduction in the latter sub-groups compared with the tone-only group was specifically due to OC pathways.

Lesioning the COC pathway confirmed UOC pathways were likely solely responsible for TTS exacerbation and COC pathway solely for TTS reduction. TTSs in all COC− primed ears

**FIG. 5.** Differences in TTSs as indices of effects of different efferent components with priming. (See text of details of groups used to calculate differences.) Positive differences indicate increases in TTSs and negative differences indicate reductions in TTSs. Each panel presents data for a different delay between primer and tone. In each panel the full line (“All OC effects”) shows the effect of all OC pathways, open symbols show the effect of UOC pathways alone (“UOC-alone” effects), and closed symbols the effects of the COC pathway alone (“COC-alone” effects). For 400-s delay, differences were calculated separately for exacerbated and protected OC+ subgroups and are shown in D. 1 (exacerbated subgroup) and 2 ("protected" subgroup). (Only OC+ data for this delay showed this division into exacerbated and protected subgroups: all OC− ears with this delay showed the same effect as did all COC− ears. Hence, in D, 1 and 2, difference curves for “UOC alone effects” and "noise alone effects" are the same.) The hatched region always represents ±4 dB around 0 dB difference; generally differences <4 dB were not statistically significant.
(n = 6) were similar to TTSs in the exacerbated OC+ subgroup (Fig. 4D3, Δ; condition and interaction P > 0.9) and differed in the same way as that subgroup from the tone-alone group (Fig. 4D1), the “protected” OC+ subgroup (Fig. 4D3, open circles), and the OC− primed group (Fig. 4D2). The fact that all OC− animals showed exacerbated TTSs appears different from effects in OC+ ears where 4/7 animals showed exacerbated TTSs and 3/7 showed reduced TTSs (protection). However, the distribution of exacerbated and protected subgroups in OC+ and OC− ears was not different, just failing to achieve significance (χ² = 3.34, df = 1, P > 0.05), perhaps because of the small n.

Difference curves were separately constructed for exacerbated and protected sub-groups. (For both groups, only OC+ data differed, since all OC− and COC− ears here showed the same effects.)

In the exacerbated subgroup (Fig. 5D1), UOC pathways were responsible for all TTS exacerbations and there was no COC pathway modulation of TTSs. Exacerbation ≥5 dB occurred from 16 to 24 kHz, with peak exacerbation of ~12 dB fairly uniformly from 18 to 22 kHz.

In the protected OC+ subgroup (Fig. 5D2), intact OC pathways reduced TTSs by ≥5 dB at all frequencies from 11 to 28 kHz, with a peak reduction of ~17 dB at 15 kHz declining to <15 dB beyond 16 kHz and <10 dB beyond 22 kHz (All-OC effects, line). Whether this was the totality of COC pathway protection depended on interpretation of further analyses. As noted in the preceding text, for this priming delay all OC− and COC− animals showed the same effects, suggesting that in all animals, UOC pathways could have been acting in the same way, with the only difference between exacerbated and protected OC+ subgroups being due to the COC pathway. Thus even in the protected OC+ subgroup, UOC pathways could have been exacerbating TTSs. This UOC-alone effect, calculated again as the difference between OC− and COC− ears, is also shown in Fig. 5D2. If this UOC exacerbating effect was present in the protected OC+ subgroup, then COC protection must be much larger than the all-OC effect calculated prior to the following test: to produce the latter protection, the COC pathway would have to also negate the exacerbative effect of UOC pathways. This can be seen when COC protection is indexed (as usual) from the difference between COC− data and protected OC+ data (Fig. 5D2; COC-alone effect). Now protection >10 dB occurred from 11 to 26 kHz. Peak protection was ~25 dB at 18–20 kHz with protection declining to <15 dB only beyond 20 kHz and <10 dB only beyond 26 kHz.

Thus in the 400-s priming test condition, in some animals only UOC pathways appeared active and then exacerbated TTSs from the peak-affected frequency to higher frequencies. In others, COC pathways were active and reduced TTSs at most tone-affected frequencies to below the unprimed tone-only group. In these animals, if UOC pathways exercised the same effect as in the exacerbated subgroup, COC pathways negated this effect and, additionally, further reduced TTSs. Then in the protected subgroup, the COC pathway may have protected by as much as 25 dB.

SIX-HUNDRED SECOND DELAY RESETS ALL OC ACTIONS. Priming with 600-s delay did not cause noise exacerbation or OC modulation of TTSs, which were similar in OC− primed ears (Fig. 3E), OC+ primed ears (Fig. 2F), and in the tone-only group. Lesioning the COC pathway also did not show any “hidden” OC effect (viz., 5-s delay). TTSs in COC− primed ears (Fig. 4E; n = 5) were similar to those in the tone-only (condition P = 0.37, interaction P = 0.07), OC− primed (Fig. 4E2; condition P = 0.41, interaction P = 0.79), and OC+ primed (Fig. 4E3; condition P = 0.57, interaction P = 0.99) groups.

Comparison of efferent effects across priming delay

A final comparison of primed OC+ ears was made, across delays from 80 to 400 s, of TTSs reduced (protected) or exacerbated compared with the tone-only group. With respect to protected TTSs, data at 80-s delay was compared with data from the single animal (1/6 animals) at 300-s delay that showed protected TTSs and to data from the protected subgroup (3/7 animals) with 400-s delay. Statistical comparisons made between the 80- and 400-s groups found no difference (P > 0.25 for condition and interaction factors). Data from the protected animal at 300 s were in the range for the other two groups. For cases with exacerbated TTSs, pair-wise comparisons between the group with 200-s delay, exacerbated subgroup (5/6 animals) at 300-s delay, and exacerbated subgroup (4/7) at 400-s delay found no differences (P always more than 0.4 for condition and interaction factors). Thus for priming delays from 80–400 s, when TTSs were reduced from the tone-only group, they remained at the same low level across delay, and when increased above the tone-only group, they remained at the same high level across delay. The significance of these data are discussed later.

Effects of noise priming on CAP thresholds

In 40 animals with priming delay ≥200 s, CAP thresholds from 9 to 28 kHz were re-measured between primer and loud tone, generally starting 5–8 s postprimer. CAP thresholds were unaltered except in six animals in which there was a small transient 5–6 dB elevation of thresholds at the first test frequency postprimer but not at any other frequency or even at the first-tested frequency when re-tested (within 30 s of the 1st measurement). In the six animals, this frequency, in the range 12–18 kHz, was measured within 5 s postprimer. In other animals in which such early measurement was made, no such effect was seen even at the first frequency re-measured postprimer. Thus generally, the noise primer appeared to have no effect on CAP thresholds; these results are therefore not illustrated.

D I S C U S S I O N

Since lesions were always made prior to priming, this study did not determine whether priming directly activated OC pathways or whether it “primed” these pathways for activation by the subsequent loud tone. This could be addressed by varying the timing of lesions, and will be examined in later studies.

As noted in results, noise priming caused two general effects. First, the primer had “pure” cochlear-only effects that exacerbated tone-induced TTSs. Second, after priming, COC and UOC pathways could reduce (protect) or increase (exacerbate) tone-induced TTSs compared with TTSs caused by an unprimed tone-only exposure. These two general effects are distinguished in this discussion.
Noise priming and exacerbation of loud-tone-induced TTSs

This study and the parallel one (Rajan 2000) show (from effects seen in OC− ears) that noise can exert a cochlear effect that exacerbates loud tone-induced TTSs. This was greatest (Fig. 3E) when noise was concurrent with loud tone (Rajan 2000), and then tone-induced TTSs were exacerbated at frequencies on either side of the peak tone-affected frequency, by greater amounts on the high-frequency side than at lower frequencies. With delays between noise and tone (this study), this effect only occurred at frequencies higher than the peak tone-affected frequency and declined rapidly with delay, being absent for delay ≥200 s. Noise itself did not cause TTSs in this or the parallel study (except inconsistently, here, at one variable frequency in 6 of 40 ears).

Using free-field conditions, Kujawa and Liberman (1997) found, in OC− ears, long-term conditioning over many days with low-level narrowband noise elevated PTSs to subsequent trauma of the same noise at a high-level, compared with PTSs in unconditioned trauma-alone ears. This occurred at frequencies higher than the exposure band (cf. Fig. 6A in Kujawa and Liberman 1997) and is equivalent to the effect here despite different exposure laterality conditions (free-field/binaural vs. the present monaural condition). Kujawa and Liberman report their exacerbative effects in OC− ears (ears effectively monaural with respect to centrifugal influences). For the unprimed monaural tone-only exposure here (Rajan 2000), OC− ears are equivalent to OC+ ears and TTSs are similar. Hence comparison of primed OC− ears here to either OC+ or OC− unprimed monaural-exposure ears would show priming has “pure cochlear” deleterious effects on TTSs. Thus this exacerbative effect appears to occur whether trauma causes TTSs (present study) or PTSs (Kujawa and Liberman 1997) and despite differences in spectra of conditioner/primer and later loud sound and time course of conditioning. Exacerbative effects of conditioning on PTSs and morphological damage caused by terminal trauma were also reported (Subramaniam et al. 1993) with long-term free-field low-frequency conditioning followed by higher-frequency terminal trauma but not (Campos et al. 1991) when conditioner and terminal trauma had the same frequency content. The former study has some analogy here in that different sounds were used for conditioning and terminal trauma. However, given the broadband primer here included the terminal trauma frequency and that Kujawa and Liberman (1997) found exacerbative effects when conditioner and primer were identical, a difference in exact frequency content of primer and terminal loud tone is unlikely to be relevant in exacerbative primer effects here. The mechanism of such prolonged exacerbative effects of a nontraumatic primer remains to be elucidated (Rajan 2000).

Efferent components involved in priming effects on TTSs

Priming elicited complex OC end effects on TTSs, and both UOC and COC pathways could moderate TTSs for priming delays <600 s. These effects will be treated as a continuum from effects seen when monaural noise was concurrent with monaural loud tone (Rajan 2000). It is likely that OC effects here are due to only to MOC efferents. The COC pathway consists almost exclusively of the CMOCs, and therefore this system must mediate COC pathway effects here. UOC pathways consist almost exclusively of the CMOCs, and the LOCS terminating on OHCs, and the LOCs terminating on dendrites of afferent neurons. TTSs measured 5 min postexposure (as here) appear due to only OHC effects (Patuzzi et al. 1989). UOC effects on TTSs here must therefore be exercised at OHCs, implying they are exercised specifically through the UMOCs component. It is also difficult to see how LOCS actions at afferent dendrites could reduce TTSs (this study) or prevent noise from exacerbating loud-tone-induced TTSs (Rajan 2000). Support for attributing TTS-modulating effects of UOC pathways to the UMOCs comes from the observation (with 5-s priming delay) that the CMOCs blocked a protective effect of UOC pathways. The selective lesion that revealed this effect interrupted only CMOCs fibers along their course at some distance from the cell bodies and therefore would not prevent interactions between UOC and COC systems at the cell bodies. A blocking effect at the latter level should still have been present when only the COC pathway was lesioned. Since this was not the case, the COC block must prevent UOC actions at the cochlea, suggesting that these CMOCs and UOC effects are exacerbated at the same site, namely OHCs. For these reasons, UOC effects seen here will be attributed to the UMOCs.

Priming and UMOCs modulation of TTSs

When monaural noise and tone were concurrent (Rajan 2000), only UOC pathways exercised effects and prevented noise exacerbation of TTSs but did not reduce TTSs below those to tone alone. It was concluded (Rajan 2000) that UMOCs acts on the mechanism whereby noise exacerbates tone-induced TTSs rather than the mechanism(s) whereby sound causes TTSs. With priming, UOC pathways can act on the TTS mechanism(s) and reduce or exacerbate TTSs compared with tone-alone TTSs.

For short priming delays when noise had a persistent, decreasing, exacerbative effect on tone-induced TTSs, the UMOCs could prevent this noise effect. However, with a very short priming delay of 5 s, this UMOCs effect was blocked by the CMOCs and was observed only after COC pathway lesion. With a longer delay of 80 s, this UMOCs effect was present; further the UMOCs worked with the CMOCs to reduce TTSs to below those to a monaural unprimed loud tone. For longer priming delays, at which the noise exacerbative effect was absent, the UMOCs only increased tone-induced TTSs with the proportion of animals so affected decreasing with delay (200 s: 5/5; 300 s: 5/6; 400 s: 4/7). (Although 300-s delay was not tested with selective de-erettention, testing with 200- and 400-s delays suggested that for delays >80 s, TTS exacerbation was likely due to UOC pathways alone.) This difference is unlikely to be due to two different UMOCs actions on OHCs. OHCs possess nicotinic- and muscarinic-type ACh receptors (e.g., reviews by Guth and Norris 1996; Puel 1995), but both cause OHC hyperpolarization (albeit on different time scales) and MOCS effects at the cochlea are relatively stereotyped (reviews by Guinan 1988; Weiderhold 1986). The most likely hypothesis is that with respect to TTSs, the UMOCs exerted only one action “designed” to work against the mechanism whereby noise exacerbates tone-induced TTSs. For the 15-min-long noise and loud tones of the parallel (Rajan 2000) and present studies, this noise exacerbation is present only for delays ≥80 s. For delays <80 s, UMOCs effects only prevent
the noise exacerbative effect rather than modulate tone-induced TTSs. The 80-s priming delay represents a “cross-over” point where noise exacerbatation of TTSs is present but weak, and UMOCs actually reduces tone-induced TTSs. [Note that with concurrent noise + loud tone (Rajan 2000), the UMOCs effect is strong and prevents noise exacerbatation of TTSs by ≈25 dB (at 20–22 kHz). As noise exacerbatation waned, the same strong UMOCs action may reduce pure tone-induced TTSs. This would account for the fact that with 80-s priming delay, where noise exacerbatation of TTSs was small the UMOCs contributed with the CMOCs to significant reduction in TTSs in OC+ ears.]

To account for effects at priming delay ≥200 s, it is postulated that when the same UMOCs action occurs in the total absence of the mechanism whereby noise exacerbates tone-induced TTSs, it exacerbates TTSs and is the sole UMOCs effect at priming delay ≥200 s. This persists to ≥400-s delay, and even in the protected OC+ subgroup at this delay, the UMOCs may have been exacerbating TTSs (Fig. 5D2). TTS exacerbation by UOC pathways has been reported to tone-alone exposure (Rajan 2001) in animals with a chronic partial hearing loss in one ear. There, as here, when there is no noise effect on tone-induced TTSs, UOC pathways when activated can exacerbate TTSs (Rajan 2001). As in that study, however, the mechanism of such action is unknown.

**Priming and CMOCs effects at the cochlea**

CMOCs effects on TTSs occurred with delays between monaural noise primer and loud tone (this study) but not when monaural noise and tone were concurrent (Rajan 2000), suggesting the primer may cause a slow “build-up” effect (likely facilitatory) in CMOCs cell bodies, allowing a later loud tone to activate them. Alternatively, when UMOCs end effects are dominant (as with concurrent noise and tone), they may block potential CMOCs end effects. A blocking interaction was seen between end effects of the MOC systems with 5-s delay (though then it was the CMOCs blocking UMOCs end effects on TTSs). Further, with 400-s delay, in the protected OC+ subgroup, it appeared possible that CMOCs action blocked a UMOCs exacerbative effect and, further, reduced TTSs. Such interaction may be produced through presynaptically located (on MOCs efferents) muscarinic-type receptors (Bartolami et al. 1993) suggested to function as autoreceptors that may decrease ACh release from presynaptic elements. These receptors may also be used by one MOCs component to modulate the other component. It is not yet possible to directly confirm such interactions between the two MOCs systems because it is not possible yet to selectively block (either surgically with lesions, or pharmacologically at the cochlea) the UMOCs without affecting the CMOCs.

These putative blocking interactions may account for “oscillations” in occurrence of CMOCs protection. With a very short delay of 5 s, the COC pathway blocked, either by effects exercised on to UOC efferents or through an end-effect that directly exacerbated TTSs, a UMOCs effect that would have prevented noise exacerbatation of tone-induced TTSs. Thereafter any CMOCs effects were protective and appeared exerted directly on the mechanism whereby sound causes TTSs, reducing TTSs below those to monaural unprimed loud tone. This effect appeared to oscillate, being relatively small with 80-s delay, absent for 200-s delay, and present thereafter in increasing proportion of animals (likely 1/6 for 300 s and 3/7 for 400 s). These oscillations may not have been due to waning of a dominant UMOCs end effect on TTSs. For the protected OC+ subgroup at 400-s delay, CMOCs protection may have occurred in the presence of a strong UMOCs exacerbative end effect on TTSs, equal to that with 200-s delay when only UMOCs effects occurred without any CMOCs protection. One explanation is that the UMOCs exercised an end effect on TTSs and a separate blocking effect on the CMOCs. For 200-s delay, both effects were present, and therefore the only OC effects on TTSs were UMOCs effects. Thereafter the UMOCs blocking effect on CMOCs may have waned (without any change in UMOCs exacerbative end effect on TTSs). Thus as the CMOCs was released from UMOCs block, it exerted protective effects in 1/6 cases with 300-s delay and 3/7 cases with 400-s delay. I will present evidence in a report in preparation that the UMOCs can block a CMOCs effect.

Finally, as noted in the preceding text, in the protected OC+ subgroup at 400-s delay the UMOCs may have been exercising an exacerbative effect as in the exacerbated subgroup. Then in the protected OC+ subgroup, CMOCs protection may not have been just the protection (maximally ≈18 dB) due to all-OC effects (Fig. 5D2) because the CMOCs would have to also negate the UMOCs exacerbative effect. When CMOCs protection was calculated, as in all other cases, from differences between COC− and OC+ data (Fig. 5D2), it did appear to exert a much larger protection of almost 25 dB, as large as the largest protection seen with CMOCs action to binaural (unprimed) tone (Rajan 1995b, 1996b, 2000).

**Mechanism of action of OC pathways to modulate TTSs**

With respect to protection, the UMOCs and CMOCs may act on one (the same) locus/process contributing to the overall TTS after loud sound. This is suggested by the fact that for delays from 80 to 400 s, all protected OC+ cases showed similar TTSs even though protection at 80-s delay was due to both UMOCs and CMOCs, whereas at 400 s was due to only the CMOCs. These protected TTSs were similar to TTSs (Rajan 2000) to binaural (unprimed) tone-alone exposure, when only CMOCs protects. Recent studies (Dallos et al. 1997; Ota and Dolan 2000; Reiter and Liberman 1995; Sridhar et al. 1995) show that, additional to well-described fast cochlear effects of (M)OC pathway stimulation, a slow effect is exercised through Ca2+−dependent mechanisms in OHCs. The latter has been suggested (Reiter and Liberman 1995; Sridhar et al. 1995) to be causally related to CMOCs protection from TTSs, but this is inconsistent with two observations. First, although such slow effects occur in vitro in OHCs from different cochlear regions (Dallos et al. 1997), in vivo they are negligible or absent at frequencies ≈10 kHz (Ota and Dolan 2000; Reiter and Liberman 1995; Sridhar et al. 1995). CMOCs protection from TTSs occurs for all tone exposures from 3 to 20 kHz (in a complex manner detailed in Rajan 1995b). Second, the slow effect declines with maintained MOC electrical stimulation (Sridhar et al. 1995) and is almost totally absent by the end of 5 min stimulation (Reiter and Liberman 1995). This differs from sound-evoked CMOCs protection both in regard to absolute duration required for protection to occur and trend of protection with increasing duration. For pure tone-induced
TTSs, CMOCS protection was present for 3-, 7-, or 20-kHz loud exposures for 10–40 min (depending on frequency) but not shorter duration (Rajan 1995b). For 11-, 15-, and 20-kHz exposures (Rajan 1995b), CMOCS protection increased with exposure duration from 7 to 10 min (11 and 15 kHz) or 10 to 15 min (20 kHz). These data make it questionable whether the slow MOCs effect is involved in TTS-reducing CMOCS effects. No other plausible explanation is evident for this CMOCS action, or TTS-reducing UMOCS effects (present study), or TTS-exacerbating UMOCS effects (Rajan 2001; present study). However, the present results add weight to the hypothesis (Rajan 2001) that UMOCS and CMOCS can exert different effects at the one cochlear locus, the OHCs, because the former could exert exacerabative effects not seen with the latter.

**Primbing and activation of UMOCS fibers**

This study and the parallel one (Rajan 2000) show that UOC pathways (presumed UMOCS) can modulate TTSs when noise and loud tone (concurrent or consecutive) are in their projection ear alone. This challenges the view that UOC neurons (most likely UMOCS neurons) are driven by the ear other than that to which they project (Liberman and Brown 1986) and facilitated by noise in the projection ear (Brown et al. 1998; Liberman 1988). Liberman (1988) has described prolonged facilitatory aftereffects, outlasting the stimulation period, of noise on single efferent neural responses to tones. Such effects have correspondence to the present effects, but linkages have to be made cautiously. In Liberman’s study, aftereffects (as opposed to within-stimulation period effects) were reported to occur only when noise was at high levels, particularly levels causing TTSs, whereas I report OC effects with priming noise that did not cause TTSs. Second, aftereffects in Liberman’s study may not have occurred at frequency ranges under study here. Liberman did not report on a relationship between prolonged aftereffects and characteristic frequency (CF) of efferent neurons. However, for within-stimulation period effects, Liberman (1988) reported that only very high CF efferent neurons were facilitated by noise in the same ear as tones to which the neuron responded, and Fig. 9 of Liberman (1988) suggests this occurs for neurons with CF >20 kHz. In the present study, efferent aftereffects with the primer noise + later tone condition in the same ear were seen at lower (CAP) frequencies. Nevertheless effects such as those described by Liberman must play a role in effects in this study.

**Comparison to other studies of conditioning**

Previous studies of conditioning stereotypically found protection from damage caused by a terminal trauma (e.g., Campo et al. 1991; Canlon 1996; Canlon et al. 1988; Kujawa and Liberman 1997; Miyakita et al. 1992; Ryan et al. 1994; Subramaniam et al. 1996; Zheng et al. 1997b). Methodological differences between the present study and these studies [using free-field (binaural) sounds, long-term (i.e., many repeated) conditioning sessions] qualify direct comparisons. Furthermore this study used terminal trauma causing TTSs, whereas previous studies used trauma causing PTSSs and/or morphological damage, and PTSSs have been suggested (Liberman et al. 1986) to be due to different mechanisms than TTSs (Patuzzi et al. 1989). Finally the present study was carried out with priming under deep anesthesia unlike long-term conditioning studies, and this may also have implications for expression of conditioning-related protection.

Nevertheless, some effects in this study (the first to systematically examine effects of a wide range of delays between conditioner/primter and trauma) also appear to occur for PTSSs with conditioning. TTSs could be exacerbated by priming, as also appears to occur for PTSSs with conditioning (Kujawa and Liberman 1997). Furthermore there are suggestions, for some sounds, that protective or exacerabative effects may occur at different delays after long-term conditioning. Long-term free-field conditioning with octave-band noise at 4 kHz reduced PTSSs and morphological damage when the terminal same-frequency trauma was 18 h after the last conditioner but exacerbated PTSSs and morphological damage when the trauma was 5 days postconditioning (Subramaniam et al. 1996). Given these points of concurrence, the present study makes it imperative for a detailed time course study to be carried out with long-term conditioning before it can be stated definitively that conditioning provides a valuable tool for ameliorating hearing damage. Because long-term conditioning studies have used repeated conditioning sessions over days/weeks, this time-scale postconditioner may be needed for equivalence to the present study using a single 15-min-long primer and delays ≤10 min postprimer.

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