Research Article

Effects of Contralateral Acoustic Stimulation on Spontaneous Otoacoustic Emissions and Hearing Threshold Fine Structure

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ABSTRACT

Medial olivocochlear (MOC) influence on cochlear mechanics can be noninvasively, albeit indirectly, explored via the effects of contralateral acoustic stimulation (CAS) on otoacoustic emissions. CAS-mediated effects are particularly pronounced for spontaneous otoacoustic emissions (SOAEs), which are typically reduced in amplitude and shifted upward in frequency by CAS. We investigated whether similar frequency shifts and magnitude reductions were observed behaviorally in the fine structure of pure-tone hearing thresholds, a phenomenon thought to share a common underlying mechanism with SOAEs. In normal-hearing listeners, fine-resolution thresholds were obtained over a narrow frequency range centered on the frequency of an SOAE, both in the absence and presence of 60-dB SPL broadband CAS. While CAS shifted threshold fine structure patterns and SOAEs upward in frequency by a comparable amount, little reduction in the presence or depth of fine structure was observed at frequencies near those of SOAEs. In fact, CAS typically improved thresholds, particularly at threshold minima, and increased fine structure depth when reductions in the amplitude of the associated SOAE were less than 10 dB. Additional measurements made at frequencies distant from SOAEs, or near SOAEs that were more dramatically reduced in amplitude by the CAS, revealed that CAS tended to elevate thresholds and reduce threshold fine structure depth. The results suggest that thresh-

old fine structure is sensitive to MOC-mediated changes in cochlear gain, but that SOAEs complicate the interpretation of threshold measurements at nearby frequencies, perhaps due to masking or other interference effects. Both threshold fine structure and SOAEs may be significant sources of intersubject and intrasubject variability in psychoacoustic investigations of MOC function.

Keywords: threshold fine structure, spontaneous otoacoustic emissions, medial olivocochlear system, contralateral acoustic stimulation

INTRODUCTION

The sensitivity and dynamic range of the inner ear are modulated by an extensive system of efferent neural projections. In particular, the nerve fibers of the medial olivocochlear (MOC) system, originating from the superior olivary complex, provide inhibitory control of cochlear mechanics via direct synapses on the outer hair cells (OHCs) of either the ipsilateral or contralateral cochleae (reviewed in Guinan 2006; Robles and Delano 2008; Guinan 2010). Stimulation of the MOC system reduces basilar membrane motion (Murugasu and Russell 1996; Dolan et al. 1997) and, consequently, auditory nerve activity (Galambos 1956; Wiederhold and Kiang 1970) via modulation of the OHC-mediated feedback mechanism (i.e., the “cochlear amplifier”; Davis 1983). This efferent modulation has been proposed to aid in the detection of signals in background noise (Nieder and Nieder 1970a, b; Winslow and Sachs 1987; Kawase and

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Lieberman 1993; Kawase et al. 1993), protect against acoustic trauma (Cody and Johnstone 1982; Rajan and Johnstone 1988; Kujawa and Liberman 1997; Maison et al. 2013), and mediate selective attention (Scharf et al. 1997; Delano et al. 2007), although its primary functional role is still the subject of speculation.

MOC influence on cochlear mechanics may be noninvasively, though indirectly, explored via measurement of otoacoustic emissions (OAEs) (Mountain 1980; Siegel and Kim 1982). OAEs are sounds recorded in the ear canal (Kemp 1978) that originate as a by-product of cochlear amplification and are sensitive indicators of OHC function. While MOC modulation of OAEs evoked by clicks or tones is typically quite small, with amplitude reductions on the order of a few decibels or less, more pronounced effects are observed for spontaneous OAEs (SOAEs), narrowband cochlear signals measured in the absence of an evoking stimulus. Activation of the MOC system via contralateral acoustic stimulation (CAS) reduces SOAE amplitudes by as much as 15 dB and produces small upward shifts in SOAE frequencies (Mott et al. 1989; Harrison and Burns 1993; Zhao and Dhar 2010). SOAE frequency shifts may be related to the phase leads observed in evoked OAEs (Francis and Guinan 2010) and in direct measurements of basilar membrane motion (Cooper and Guinan 2003) with MOC activation.

Here, we examine whether CAS-mediated magnitude reductions and frequency shifts are also evident for a behavioral phenomenon termed threshold fine structure, i.e., quasiperiodic fluctuations in hearing sensitivity across frequency (Elliott 1958). This fine structure is thought to be intrinsically related to OAE generation, particularly to the mechanisms underlying SOAE generation. More specifically, threshold fine structure is proposed to arise via a cochlear resonance phenomenon, whereby a portion of the OAE initiated by the test tone undergoes multiple reflections between its generation site and the middle ear boundary (Kemp 1979a; Talmadge et al. 1998; Epp et al. 2010). Cochlear responses are enhanced at frequencies for which the round-trip delay of the forward and reverse traveling OAE energy is an integer number of cycles, producing local peaks in sensitivity (i.e., threshold minima). Provided sufficient round-trip amplification, self-sustaining standing waves are generated at these same frequencies, which may be detected in the ear canal as SOAEs (Kemp 1979b; Wilson 1980; Zwicker and Schloth 1984). The frequency correspondence between SOAEs and threshold minima, as well as the common dependence of these phenomena on cochlear amplification, has been demonstrated experimentally (Long and Tubis 1988a, b; Furst et al. 1992).

While CAS is known to elevate behavioral hearing thresholds (e.g., Wegel and Lane 1924; Ingham 1957; Zwislocki et al. 1967; Kawase et al. 2003), the effects of CAS on threshold fine structure have not been explored. Such effects would provide a behavioral confirmation of the magnitude and frequency shifts observed for SOAEs, as well as a potentially sensitive behavioral measure of MOC-induced changes in cochlear function. Conversely, such shifts could contribute significant variability in psychoacoustic measures of MOC effects either across frequency or across individuals. Just as MOC effects on OAEs are known to fluctuate with frequency (e.g., Siegel and Kim 1982; Guinan 1986; Sun 2008; Abdala et al. 2009), the effects of CAS on behavioral thresholds may also exhibit fine structure. Understanding such complexities may aid in refining attempts to relate MOC-mediated changes in OAEs with performance on psychoacoustic tasks (e.g., Micheyl et al. 1995a, b; Garinis et al. 2011).

In the present study, we examined the effects of CAS on pure-tone thresholds measured at frequencies immediately near those of SOAEs in normal-hearing participants. Although threshold fine structure is potentially measurable in the absence of SOAEs (Zwicker and Schloth 1984), we focused our measurements on SOAE frequencies so as to reliably locate threshold minima and to make precise comparisons between magnitude and frequency shifts in the SOAE and behavioral measures. However, this approach was complicated by the perceptual effects associated with SOAEs. SOAEs interact with external tones at nearby frequencies to produce perceptions of beating and roughness (Wilson 1980; Long and Tubis 1988a; Long 1998) and may also cause masking or adaptation (Long and Tubis 1988a, b; Smurzynski and Probst 1998). Indeed, we found that the presence of SOAEs produced unanticipated CAS-mediated effects on both threshold levels and fine structure magnitude. Therefore, additional threshold measurements were made at frequencies distant from SOAEs for comparison.

METHODS

Subjects

Twenty-two normal-hearing individuals without history of ear pathology were recruited for participation. All had pure-tone thresholds less than or equal to 20-dB hearing level (HL) at octave frequencies from 0.25 to 8 kHz, as well as at 3 and 6 kHz, measured using an Interacoustics Audio Traveller AA220 (Interacoustics, Assens, Denmark). Normal middle ear function was verified using a GSI Tympanometer Middle Ear Analyzer (Grason Stadler Inc., Eden Prairie, MN).

Of the initial recruits, four did not complete the experiment, and two were excluded from analysis due to excessive variability in either the SOAE or threshold measurements. Data from 16 subjects (14 female, 2 male) between 20 and 45 years old (mean=25 years) are presented here. Three of these subjects were associated with the laboratory (including first and second authors) and volunteered their time. The remaining subjects provided written, informed consent and were compensated monetarily. All procedures were approved by the Institutional Review Board at Northwestern University.

Instrumentation and Calibration

All measurements were made in a sound-treated audiometric booth. Signals were generated and recorded using custom software written in C++ run from an Apple Macintosh computer, with digital-to-analog and analog-to-digital conversion performed by a MOTU 828mkII FireWire interface (Mark of the Unicorn, Cambridge, MA) using a 44.1-kHz sampling rate and 24-bit resolution. Outgoing signals were amplified (Etymotic Research ER H4C, Elk Grove Village, IL) and presented via MB Quart 13.01 HX drivers (Maxxsonics, Chicago, IL). The drivers were coupled to the ear canal using either an Etymotic Research ER-10B+ probe assembly (for the test ear) or with plastic tubing connected to an ER3-14A foam ear tip (for the contralateral ear). SOAE recordings were obtained from the test ear using the ER-10B+ microphone and preamplifier (20-dB gain), with signals digitized by the MOTU and saved for offline analysis.

An in situ calibration procedure was used to compensate for the effects of probe insertion depth and the frequency response of the transducers, ensuring that stimuli were delivered to the eardrum at a uniform level (Lee et al. 2012). At the beginning of each test session, the depth of probe insertion was determined from the half-wave resonance peak of the ear canal response to a slow chirp (0.2–20 kHz), normalized to the chirp response in a long lossy tube (50 ft long, 0.375 in outside diameter, copper tubing). Chirp responses previously obtained at various probe insertion depths in a Brüel & Kjær (Nærum, Denmark) 4157 ear simulator (IEC 60318-4) were then used to derive frequency-specific compensation factors appropriate for the depth of the probe in the subject's ear canal. These factors were applied to all stimuli subsequently presented to the test ear. Stimuli presented to the contralateral ear (i.e., broadband noise) were uncompensated.

Protocol

Pure-tone thresholds and SOAEs were measured for two conditions: (1) in quiet and (2) with 60-dB SPL

broadband (0.1–10 kHz) noise presented to the contralateral ear (CAS condition). For each condition, thresholds were measured in a continuous 20–30-min block, with SOAE measurements made immediately before and after the threshold measurement block. All measurements were repeated in a second test session, with sessions typically separated by no more than 1 week. Condition order (quiet-CAS or CAS-quiet) was alternated across sessions.

SOAE-Specific Measurements

To provide detailed comparisons of CAS-mediated changes in SOAEs and thresholds, twelve female subjects completed “SOAE-specific” threshold measurements. For each subject, an SOAE that could be reliably measured in quiet and with CAS was selected for more detailed investigation. Thresholds were subsequently obtained at 25 frequencies spanning a 0.136-octave range centered on the selected SOAE frequency, both in quiet and with CAS. This frequency span was chosen in order to characterize the threshold minimum (presumably occurring at or near the SOAE frequency), as well as the two adjacent threshold maxima. The frequency spacing between adjacent test points was 1/500th of an octave for the first four test points on either side of the center frequency, 1/200th of an octave for the next four points, and 1/100th of an octave for the last four points. This graded frequency resolution was chosen to more precisely estimate the frequency and level of the threshold minimum, where threshold level changes rapidly with frequency, while also providing a reasonable estimate of threshold levels at the maxima, where the rate of change in threshold levels is more gradual.

Due to the variability in the frequency of an individual SOAE between the quiet and CAS conditions, as well as across sessions, the center frequency used for the threshold measurements was always based on the SOAE frequency estimate obtained immediately prior to the threshold measurement. Thus, thresholds were rarely obtained at precisely the same frequencies between conditions or sessions, although the shift in center frequency was usually less than 10 Hz. Since all SOAE-specific measurements maintained the same relative frequency spacing (on a logarithmic frequency scale), threshold curves could still be compared between conditions and averaged across sessions. The assumption that the threshold fine structure pattern would shift in frequency with the SOAE was supported by preliminary measurements as well as the final data presented here. No attempt was made to control for potential changes in the fine structure pattern due to changes in SOAE level across days.

SOAEs were selected so as to survey a wide range of frequencies and levels, as well as CAS-mediated effects. The frequencies and levels of all twelve selected SOAEs, both in quiet and with CAS, are shown in panel B of Figure 1. For clarity, changes in SOAE frequency and level with CAS are shown in panel C. Ear canal spectra in quiet and CAS for one subject are also shown in panel A, demonstrating the typical CAS-mediated reduction in SOAE amplitude and upward shift in SOAE frequency. These changes were representative of the effects observed on the total population of SOAEs from which the selected SOAEs were taken and are consistent with previous reports of the effects of CAS on SOAEs (Mott et al. 1989; Harrison and Burns 1993; Zhao and Dhar 2010, 2011, 2012).

While we were principally interested in relating changes in thresholds with the behavior of only the selected SOAE, subjects often had multiple SOAEs near the frequency range of interest. To minimize the relative influence of adjacent SOAEs, the selected SOAE was required to have a spectral peak at least 10 dB above those of any SOAEs within a fifth-octave span. Of the seven such adjacent SOAEs detected (in six subjects), all had spectral levels of less than -10 dB SPL.

Non-SOAE-Specific Measurements

To demonstrate the effects of CAS on thresholds across a wider range of frequencies, both near and far from those of SOAEs, additional measurements were completed in six subjects (two male, four female). Two subjects (04MR and 10FR) had no measurable SOAEs, one subject (11MR) had several small (-16 to -20 dB SPL) SOAEs between 3.5 and 5 kHz, and the remaining three subjects (08FR, 15FR, and 17FL) had multiple SOAEs. Of these, 08FR and 15FR also completed an SOAE-specific threshold measurement.

For each test session, thresholds were measured at 25 frequencies in 1/100th-octave steps, covering a quarter-octave range. All measurements were repeated in a second test session, with condition order

alternated between sessions, as in the SOAE-specific measurements. For three subjects (04MR, 08FR, 17FL), this process was repeated until average threshold curves had been obtained for a two-octave range between 1 and 4 kHz (requiring approximately 20 test sessions each). Frequency lists for adjacent frequency regions overlapped by five test points (1/20th of an octave) in order to create smooth transitions between individual quarter-octave test regions in the final threshold curve. For the three other subjects, thresholds were obtained in an exploratory fashion for separate quarter-octave ranges. Representative and relevant portions of this data are presented here.

Threshold Measurements

Thresholds were obtained using a modified fixed-frequency Békésy tracking procedure (Lee et al. 2012). Stimuli were pulsed tones (250-ms duration, 25-ms rise and fall times) presented twice per second. Subjects were instructed to press a button as long as the stimulus was audible and to release the button when it was not. Presentation level was decreased if the button was pressed and increased if the button was not pressed, with each press or release of the button considered a "reversal." Starting at 30 dB SPL, presentation level was changed at the rate of 6 dB per stimulus (12 dB/s). After the first two reversals, presentation level was changed at the rate of 2 dB per stimulus (4 dB/s), and the presentation levels at the midpoints between reversals were calculated for each subsequent ascending run. This adaptive procedure continued for a minimum of four more ascending runs until the standard error of the mean midpoint value fell below 1 dB. Threshold was then defined to be the mean midpoint level.

To obtain the most accurate threshold measures, no maximum number of reversals was set. If a subject reported a lapse in attention or was responding inconsistently, he or she was instructed and the threshold tracking procedure was started again. Most subjects were able to complete the threshold mea-

FIG. 1. **A** Ear canal spectra showing the selected SOAE for one subject in quiet and with CAS. **B** Frequency and level of the twelve SOAEs chosen for study in the SOAE-specific measurements in quiet (blue circles) and with CAS (red squares). Solid lines connect the

frequencies/levels of the same SOAE in the two conditions. **C** CAS-mediated changes in the frequency (as a percentage of the frequency in quiet) and level of each SOAE.

surements at all frequencies without restarting. Test frequencies were presented in random order, so as to minimize any systematic influence of fatigue or inattention. Although the tracking procedure does not eliminate subject response bias, which may fluctuate with attention, more rigorous measurement procedures (such as a three-alternative forced choice paradigm) would be prohibitively time-consuming given the number of test frequencies for each condition.

SOAE Measurements

Two-minute ear canal recordings were obtained immediately prior to and after each block of threshold measurements. For each recording, a fast Fourier transform (FFT) of every second was calculated to produce 120 amplitude spectra. The median amplitude at each frequency bin was then used to generate the final ear canal spectrum. SOAE level and frequency were taken to be those of the 1-Hz-wide bin with the maximum spectral amplitude nearest the expected frequency.

For the first SOAE measurement in each condition, recordings commenced after 1 min of quiet or CAS. This provided time for SOAEs to settle or for the effects of CAS to plateau. SOAE measurements were intended to estimate the state of the SOAE during the block of threshold tracking, although the accuracy of this estimation was not explicitly tested. Incorporating additional SOAE measurements throughout the threshold tracking procedure was avoided, as this would have added a considerable amount of time and potentially compromised the comfort or concentration of the subject during threshold measurements. As such, any drift or variation in SOAE frequency and amplitude over time may have influenced the measurements.

Middle Ear Muscle Reflex Test

A middle ear muscle reflex (MEMR) in response to the CAS could potentially confound both the threshold and SOAE measurements by altering forward and reverse middle ear transmission. Thus, during each test session, absence of significant MEMR in response to the 60-dB SPL CAS was verified using a procedure described in Zhao and Dhar (2010) and Deeter et al. (2009). Briefly, a 602-Hz, 60-dB SPL probe tone was presented to the test ear for 4 s, with a 500-ms burst of CAS presented after the first second. The level of the CAS ranged from 50 to 80 dB SPL in 10-dB steps. Responses to five repetitions of each CAS level were averaged, and the pressure at the probe frequency was estimated as a function of time using a least-squares fit analysis of the averaged waveform (Long and

Talmadge 1997). MEMR threshold was defined as the lowest CAS level producing a change in probe tone level and/or phase that was time-locked to the presentation of the CAS. MEMR thresholds were collected during an initial screening session, as well as during all subsequent test sessions, with the exception of two occasions (for two different subjects), when time limitations precluded obtaining MEMR thresholds during the test session. However, across all screening and test sessions, at least two MEMR threshold estimates were obtained for each subject. All MEMR thresholds were 70 dB SPL or higher.

Analysis

For the SOAE-specific measurements, threshold curves were parameterized in order to calculate CAS-mediated changes in (1) threshold minimum frequency, (2) threshold minimum level, (3) threshold maxima level, and (4) fine structure depth. First, each threshold curve was smoothed using a three-point moving average. The frequencies and levels of the low- and high-frequency threshold maxima were then identified as those corresponding to the highest smoothed threshold level below and above the center frequency, respectively. Lastly, the frequency and level of the threshold minimum were taken as those corresponding to the lowest smoothed threshold between the two maxima frequencies. Fine structure depth was calculated as the difference between the smoothed threshold level at the minimum and the average smoothed threshold levels at the two maxima. The parameters for the individual threshold curves were averaged across sessions for each condition, and CAS-mediated effects were quantified as the difference between these averaged values.

Visual inspection confirmed that the minima and maxima identified by this automatic process were similar to those estimated by subjective judgments for all but one case. For this subject, all threshold curves exhibited additional, symmetric threshold dips (minima) below and above what was subjectively judged to be the threshold minimum. Threshold measurements were centered on the frequency of a particularly large (~13 dB SPL) SOAE, and this symmetric pattern of dips around the center frequency may have resulted from complex perceptual effects (e.g., the perception of beating or distortion) due to the presence of the emission (Long 1998). Although this pattern was repeatable, the lowest smoothed threshold level occurred at different minima across conditions and sessions, producing an inconsistent estimate of the frequency shift in the threshold curve. This was corrected manually by selecting the minimum frequency to be that of the lowest smoothed

threshold level near the center minimum (i.e., the middle of the three minima) for each curve.

CAS-mediated changes in SOAEs were calculated as the difference between the average SOAE frequency and level estimates for the CAS and quiet conditions. Averages for each condition were based on four SOAE measurements (two per session, across two sessions). Linear regression fits and/or Spearman's rank correlations were used to relate CAS-mediated changes in threshold minimum frequency and SOAE frequency and to relate changes in SOAE level with changes in (1) threshold level averaged across frequency, (2) threshold minimum level, (3) threshold maxima level, and (4) fine structure depth. Paired *t* tests (two-tailed) were also used to compare parameters between conditions. *P* values <0.05 were considered statistically significant. All statistical analysis was performed using MATLAB (The MathWorks Inc., Natick, MA).

RESULTS

CAS Elevates Thresholds at Frequencies Distant from Those of SOAEs

The primary purpose of the study was to characterize the effects of CAS on thresholds and threshold fine structure at frequencies near those of SOAEs. However, to establish a baseline with which to compare these effects, we first consider cases where neither SOAEs nor prominent threshold fine structure are present. As shown in Figure 2, threshold measurements at frequencies distant from those of SOAEs confirm that the basic effect of the broadband 60-dB SPL CAS is an elevation of thresholds. Threshold measurements across a quarter-octave range are shown for each of two test sessions ("S1" and "S2") with thin solid and dashed traces, respectively, along with their average (thick trace), for three subjects (panels A–C). Representative ear canal spectra demonstrate the lack of measurable SOAE activity above the noise floor within the frequency region tested. Subjects 04MR and 10FR had no measurable SOAEs outside of the displayed frequency range, and subject 11MR had two small SOAEs more than two octaves higher.

Although the absence of measurable SOAEs does not guarantee the absence of threshold fine structure, thresholds for each subject were relatively flat across this narrow frequency range, both in quiet and with CAS. Likewise, CAS-mediated threshold changes (shown in panels D–F of Fig. 2) were fairly stable across frequency. CAS typically elevated thresholds by ~2–6 dB relative to those in quiet, with a mean elevation of 4.68 dB across all frequencies and subjects. CAS-mediated threshold elevations of ~5 dB are consistent

with those previously obtained under similar conditions (e.g., Kawase et al. 2003).

CAS Improves Thresholds at Frequencies Near Those of SOAEs

To examine the effects of CAS on threshold fine structure, thresholds were obtained for a narrow frequency range centered on an SOAE frequency for each of twelve subjects. Figure 3 shows SOAE-specific measurements for three representative subjects (06FR, 15FR, 26FR), which illustrate that the effects of CAS on thresholds near SOAE frequencies were rather complex. As can be appreciated in the data from the individual test sessions (top two panels of each column, i.e., panels A–C and D–F), threshold minima were reliably observed at frequencies near those of the SOAEs. CAS shifted SOAEs and threshold minima upward in frequency by a comparable amount, with larger shifts (~7–12 Hz) seen for subjects 06FR and 15FR and a smaller shift (~3 Hz) seen for subject 26FR. In contrast, reductions in SOAE level were not accompanied by comparable threshold elevations or reductions in the depth of the fine structure. Instead, thresholds were often *improved* with CAS, particularly near threshold minima, with improvements exceeding 10 dB at certain frequencies. Of the three subjects shown, threshold improvements were more evident for 06FR and 15FR than those for 26FR, although they could also be rather variable across sessions (for 15FR in particular). For clarity, SOAE levels in quiet and with CAS for subject 26FR are indicated by the blue and red arrows, respectively.

For each subject, the effect of CAS on thresholds varied widely across frequency. This was due to both the upward frequency shift in fine structure pattern and the modulation (typically improvement) of overall threshold sensitivity. In the bottom panel of each column of Figure 3, CAS-mediated threshold changes are plotted as a function of the octave distance relative to the SOAE frequency in the quiet condition. Threshold changes for each session (solid and dashed gray lines for S1 and S2, respectively) are shown along with their average (thick black line). For subjects 06FR and 15FR, CAS-mediated changes in thresholds oscillated from slight reductions to elevations at frequencies just lower than that of the SOAE in quiet. Larger reductions (10–12 dB) were observed at frequencies just higher than the SOAE frequency, with small or no changes at the highest frequencies tested. For subject 26FR (third column), threshold changes fluctuated around 0 dB, although the general trend was for an improvement in thresholds with CAS. Note that thresholds in quiet and CAS were usually not obtained at identical frequencies, as the measurement spans were centered on the SOAE frequency in that condition (quiet or CAS). Linear interpolation of the threshold curves at the same

FIG. 2. A–C Thresholds measured in quiet (blue) and with CAS (red) for three subjects with no measurable SOAEs within the test range. Representative ear canal spectra are shown for each condition (light blue and red traces). Thresholds measured in each of two sessions (“S1” and “S2”, thin solid and dashed traces, respectively)

are shown along with their average (thick solid trace). D–F CAS-mediated changes in threshold (CAS–quiet) for each of the individual sessions (thin and solid dashed traces, as above) and the average change (thick trace) for each subject.

frequencies was therefore required prior to calculation of the difference curves.

Reductions in thresholds with CAS were not solely a consequence of the upward frequency shift in the fine structure pattern. Thresholds in quiet and with CAS are replotted as a function of the frequency distance from the SOAE measured in the respective condition (i.e., quiet or CAS) in panels A–C of Figure 4. Plotting the data this way essentially aligns all threshold minima in frequency. Changes in thresholds calculated from the difference between the two uninterpolated, aligned curves are shown in panels D–F. Thresholds were still somewhat improved with CAS, even after eliminating the influence of any frequency shifts in the fine structure pattern. Threshold improvements of up to 5–10 dB occurred at or near threshold minima, with smaller changes at more distant frequencies (i.e., at threshold maxima). Consequently, CAS actually *increased* the depth of the threshold fine structure pattern in these subjects.

Individual and average CAS-mediated changes in thresholds are shown for all twelve subjects in Figure 5. In panel A, threshold changes were calculated at frequencies relative to those of the SOAE in quiet (as in Fig. 3), thus preserving the effect of the upward

frequency shift in the fine structure pattern. Threshold changes ranged from 14.4-dB improvements to 7.3-dB elevations and varied in magnitude by as much as 18 dB with only a 1/100th-octave change in test frequency for some subjects. In panel B, CAS-mediated changes were calculated after first aligning the threshold curves with respect to their minima (as in Fig. 4). The effects of CAS were smaller and less variable when minimizing the effect of the frequency shift, although the majority of subjects still demonstrated consistent threshold improvements. In some subjects, sensitivity improvements were observed throughout the entire 0.136-octave range, although they were still largest at the minimum, approaching 10 dB in several cases. When averaged across all frequencies, CAS-mediated threshold changes were positive for only two of the twelve subjects, with average threshold elevations of 0.33 and 1.21 dB, respectively. In no case was a uniform elevation in threshold observed.

Although qualitative appreciation of the data may be most appropriate due to the limited sample size, two-tailed paired *t* tests were performed for threshold parameters that were deemed to follow a normal distribution (via the one-sample Kolmogorov-Smirnov test implemented in MATLAB). These analyses are largely consistent with the effects that are visible in the

FIG. 3. SOAE-specific measurements in quiet and with CAS for three representative subjects. Each column contains data from a single subject plotted versus frequency distance (in octaves) from the SOAE frequency measured in quiet. The nominal SOAE frequency, f_{SOAE} , is indicated at the top of the column. Threshold curves and representative ear canal spectra from the two individual test sessions

are shown separately in panels A–C and D–F, respectively. For clarity, blue and red arrows indicate the SOAE amplitude in quiet and with CAS for subject 26FR (panels C, F). Changes in threshold (CAS–quiet) for each of the two sessions (thin solid and dashed gray lines) and their average (thick black line) are shown in panels G–I.

individual and group data: CAS significantly improved thresholds when averaged across frequency (mean = 1.66 dB, $t_{11} = 3.61$, $P = 0.0041$), with larger improvements at threshold minima (mean = 2.36 dB, $t_{11} = 3.12$, $P = 0.0097$), and smaller, nonsignificant improvements at threshold maxima (mean = 0.82 dB, $t_{11} = 1.87$, $P = 0.089$). Fine structure depth also increased significantly with CAS (mean = 1.54 dB, $t_{11} = 2.26$, $P = 0.045$).

CAS Shifts SOAEs and Threshold Minima Upward in Frequency

As expected, there was a close correspondence between the frequency of each threshold minimum (f_{Min}) and the

frequency of the associated SOAE (f_{SOAE}), both in quiet and with CAS. The difference between f_{Min} and f_{SOAE} for each subject is plotted in Hz and as a percentage of f_{SOAE} in panels A–B, respectively, of Figure 6. There was a tendency for threshold minima to occur slightly lower in frequency than the SOAE. On average, this frequency difference was quite small: –1.41 Hz or –0.07 % in quiet and –2.29 Hz or –0.14 % with CAS. The frequency differences observed in the CAS condition were statistically significant according to two-tailed, paired t tests (in Hz $t_{11} = -2.48$, $P = 0.031$; percentage $t_{11} = -2.73$, $P = 0.020$).

CAS-mediated shifts in f_{SOAE} and f_{Min} were typically small, ranging from 1.5 to 15 Hz (or 0.06–1.3 %). Consistent with the close frequency correspondence

FIG. 4. Threshold curves from the three subjects in Figure 3 replotted to minimize the effect of the frequency shift in the fine structure pattern. **A–C** Thresholds for each session (thin and dashed lines) and the two-session average (thick lines) are plotted as a function of the frequency distance from the SOAE frequency

measured in the same condition (quiet or CAS), such that all curves are aligned relative to their minima. **D–F** CAS-mediated changes (CAS-quiet) in the aligned threshold curves are shown for each session (thin and dashed lines) along with their average (thick lines).

described above, shifts in f_{SOAE} and f_{Min} were significantly linearly correlated (*in Hz* adjusted $r^2_{10}=0.67$, $P=0.00037$; *percentage* adjusted $r^2_{10}=0.52$, $P=0.0027$), as shown in panels C–D of Figure 6. The slopes of the linear regression fits (black lines) fell short of unity (dashed gray lines), perhaps due to drift in the SOAE frequency over time or due to the small number of subjects with larger frequency shifts.

Reductions in SOAE Amplitude Are Associated with Threshold Improvements

Changes in SOAE level are plotted versus changes in threshold levels averaged across all frequencies (T_{Ave}), threshold minimum level (T_{Min}), threshold maxima level (T_{Max} , averaged across both maxima), and fine structure depth (i.e., $T_{\text{Max}}-T_{\text{Min}}$) in Figure 7 (panels A–D, respec-

FIG. 5. Individual (thin gray lines) and average (thick black line) CAS-mediated changes in thresholds for all twelve SOAE-specific measurements. In **A**, threshold changes were calculated at frequencies relative to the SOAE frequency in quiet, thus preserving the effects of the frequency shift in the fine structure patterns (as in

Fig. 3). In **B**, changes were calculated after first aligning the threshold curves with respect to their minima, i.e., by plotting thresholds as a function of frequency distance from the SOAE in the same condition (as in Fig. 4).

FIG. 6. **A–B** The frequency of each threshold minimum (f_{Min}) corresponded closely with the associated SOAE frequency (f_{SOAE}), both in quiet and CAS. The frequency difference ($f_{\text{Min re } f_{\text{SOAE}}}$) is shown in Hz (**A**) and as a percentage (**B**) for each subject (*open symbols*) along with the average (*solid symbols*, $\pm$ one standard deviation). Threshold minima tended to occur slightly lower in frequency than the associated SOAE. Asterisks indicate that this frequency difference was significant at the $P < 0.05$ level according to

two-tailed, paired t tests for the CAS condition. **C–D** CAS-mediated changes in SOAE frequency (Δf_{SOAE}) were significantly linearly correlated with changes in the threshold minimum frequency (Δf_{Min}), whether expressed in Hz (**C**) or as a percentage (**D**). Adjusted r^2 values are shown in each panel with asterisks indicating significance at the $P < 0.05$ level. Solid black lines indicate the linear regression fits, and gray dashed lines are unity.

tively). While no significant Spearman's rank correlations were found when all of the data were included, larger SOAE level reductions were typically associated with greater threshold improvements, particularly at threshold minima. These trends were mainly apparent for SOAE level reductions of less than 10 dB (points to the right of the dashed vertical line in each panel), with threshold improvements saturating or reversing for the two cases with larger SOAE reductions. It is not clear if these two points are outliers or if the relationships are actually non-monotonic.

When considering only SOAE level reductions of less than 10 dB, Spearman's rank correlations indicated that larger reductions in SOAE level were associated with larger improvements in thresholds averaged across frequency ($\rho_{10} = 0.71$, $P = 0.028$), threshold minimum level ($\rho_{10} = 0.83$, $P = 0.0056$), and threshold maxima level ($\rho_{10} = 0.70$, $P = 0.031$). Larger SOAE level reductions were also associated with larger increases in fine structure depth ($\rho_{10} = -0.78$, $P = 0.012$), due to greater threshold improvements at minima than at maxima. Linear regression fits for these ten data

FIG. 7. **A–D** Relationships between CAS-mediated changes in SOAE level and changes in average threshold level (T_{Ave}), threshold minimum level (T_{Min}), threshold maxima level (T_{Max}), and threshold fine structure depth. At least for SOAE level reductions less than 10 dB (*the ten points to the right of the dashed vertical lines*), larger SOAE level reductions were associated with greater threshold improvements and increases in fine structure depth. Spearman's rank correlation coefficients calculated

for these ten data points are shown in each panel, with asterisks indicating significance at the $P < 0.05$ level. For reference, solid black lines are the linear regression fits computed for these data, and dashed gray lines are $y = x$ in **A–C** or $y = -x$ in **D**. Data from the two subjects with SOAE reductions larger than 10 dB indicate that threshold improvements may saturate or reverse with increasing CAS effects.

points (black lines) and unity (dashed gray lines) are shown for reference. These relationships are opposite to those anticipated for a simple codependence of SOAEs and threshold fine structure on cochlear gain and indicate that the presence of SOAEs complicates interpretation of the threshold measurements.

SOAEs Influence the Effects of CAS on Threshold Levels and Fine Structure

To provide a more comprehensive view of how CAS affects threshold levels and fine structure at frequencies both near and far from those of SOAEs, additional threshold measurements were

obtained in 1/100th-octave steps across a two-octave range for three subjects with different SOAE and threshold fine structure profiles. Thresholds for each subject (04MR, 08FR, 17FL) are shown in Figure 8, and the CAS-mediated changes in thresholds are plotted together in Figure 9.

Subject 04MR (Fig. 8A; black trace in Fig. 9) had no measurable SOAEs and minimal threshold fine structure. CAS elevated thresholds across the entire frequency range, with an average elevation of 3.11 dB, consistent with the results shown for subjects with similar SOAE profiles in Figure 2 (note that the first quarter-octave span of 04MR's data is also shown in Fig. 2). Threshold elevations tended to be larger at

FIG. 8. Thresholds and representative ear canal spectra for three subjects with distinct SOAE profiles and CAS-mediated threshold changes. Each subject completed threshold measurements from 1 to 4 kHz in 1/100th-octave steps over the course of approximately 20 test sessions. Threshold measurements were repeated twice, with frequency lists between sessions overlapped by five points, so that all thresholds

represent the average of two to four measurements. For subjects 08FR (B) and 17FL (C), black triangles and brackets indicate frequency regions where thresholds were improved by CAS. Blue and red arrows in subject 17FL's plot indicate the peak spectral level of an SOAE measured in quiet and with CAS, respectively. See text for further discussion.

FIG. 9. CAS-mediated changes in thresholds across frequency for the three subjects in Figure 8.

lower frequencies (1–2-kHz average=3.91 dB; 2–4-kHz average=2.31 dB). Although thresholds generally varied little across frequency, a few shallow (<5 dB), periodic ripples were observed near 2 and 4 kHz. With CAS, this fine structure appeared to be somewhat preserved near 2 kHz but reduced at 4 kHz. Interpretation of these changes is limited by the small magnitude of the threshold fluctuations and the coarseness of the measurements. The overall elevation in thresholds, however, is consistent with an MOC-induced reduction in cochlear gain.

In contrast, subject 08FR (Fig. 8B; dashed red trace in Fig. 9) possessed multiple SOAEs and pronounced fine structure within the test range. Changes in SOAE level with CAS were variable across SOAEs and between test sessions but typically ranged from 3 to 5 dB. Thresholds were *decreased* with CAS by an average of 1.40 dB across the entire two-octave range, with the most substantial threshold reductions occurring at frequencies nearest those of SOAEs (from 1 to 1.8 kHz and 2.8 to 3.2 kHz, indicated by the black triangles and brackets in Fig. 8B). Within these frequency regions, CAS consistently improved thresholds at both maxima and minima, including those not associated with an SOAE. The depth of the fine structure either remained unchanged or increased slightly. An exception to this was observed for the threshold minimum near 2.8 kHz (corresponding in frequency with a -20-dB SPL SOAE), which was elevated in level with CAS, despite the adjacent maxima being reduced in level. There was therefore a decrease in fine structure depth of ~6 dB at this minimum.

Curiously, CAS did not appear to change thresholds at frequencies more distant from those of SOAEs (see region between 1.8 and 2.8 kHz). Considering that CAS modulated SOAEs at lower and higher frequencies, it seems likely that the MOC system also inhibited OHC responses to the frequencies in between. That thresholds were unaffected may indicate that any reduction in cochlear gain was balanced by the apparent benefit of reducing nearby SOAE

amplitudes. The influence of SOAEs on thresholds may therefore extend across a considerable frequency range.

Subject 17FL (Fig. 8C; blue trace in Fig. 9) had prominent threshold fine structure but fewer SOAEs and greater CAS-mediated reductions in SOAE level than subject 08FR. The higher-level emission near 1.2 kHz was typically reduced by 15 dB (see red and blue arrows indicating SOAE level for clarity in Fig. 8C), and the next-largest emission near 1.5 kHz was reduced from 0 dB SPL to the noise floor. Data from this subject illustrate that both threshold improvements and elevations with CAS can be observed in the same ear. More importantly, this subject provides evidence that CAS does reduce threshold fine structure depth but primarily at frequencies distant from those of SOAEs, or when nearby SOAEs are largely reduced in level.

CAS improved subject 17FL's thresholds only within a narrow frequency range near the larger SOAE (marked by the black triangle and brackets in Fig. 8C). Improvements primarily occurred near the two adjacent threshold maxima with little or no change at the minimum, resulting in a decrease in fine structure depth of 3.5 dB. At all other frequencies, thresholds were elevated by approximately 2–5 dB. This was the case at frequencies near the second-largest SOAE, as well as those near the several smaller SOAEs that were barely visible above the noise floor (see small peaks near 2 and 4 kHz in the ear canal spectrum in quiet). Threshold elevations were always larger at threshold minima than at maxima, producing a reduction in fine structure depth of 1.3–6 dB (3.38 dB on average). Larger CAS-mediated reductions in fine structure depth tended to occur at lower frequencies and when the fine structure depth in quiet was large.

Data from subject 17FL provide further evidence that threshold improvements associated with reductions in SOAE level may saturate and reverse (i.e., become elevations) with larger SOAE level reductions. Threshold changes for the two “outlying” subjects in

Figure 7 (whose SOAE level reductions exceeded 10 dB) previously suggested this trend. The relationships between changes in SOAE level and threshold levels illustrated in Figure 7 may in fact be strongly curved. However, the effects of CAS on minima and maxima were rather variable for these subjects and subject 17FL. Whether thresholds are improved or elevated overall may not just depend on the change in SOAE level, but also on the absolute SOAE level in either quiet and/or CAS. For instance, despite sizable (>15 dB) reductions in the levels of both of subject 17FL's two largest SOAEs, thresholds were only elevated when the associated SOAE was reduced to the noise floor. Thus, the presence, amplitude, and frequency proximity of SOAEs, in addition to their behavior with CAS, may all influence how CAS modulates threshold levels and fine structure within a given frequency region.

DISCUSSION

Overview

We examined the effects of CAS on behavioral pure-tone thresholds at frequencies near and far from those of SOAEs, with the aims of describing MOC-mediated modulation of threshold fine structure and, conversely, the influence of this fine structure on behaviorally measured MOC effects. The primary findings were that (1) CAS produced comparable upward shifts in the frequencies of SOAEs and threshold minima; (2) CAS elevated thresholds and reduced threshold fine structure depth at frequencies distant from those of SOAEs, or when nearby SOAEs were reduced in amplitude by a large amount (>10 dB); and (3) CAS improved thresholds and increased threshold fine structure depth when nearby SOAEs were reduced in amplitude by a smaller amount. CAS-mediated changes in thresholds therefore varied widely, though somewhat predictably, across frequency and subjects.

The results suggest that threshold fine structure is sensitive to changes in cochlear gain but that this sensitivity is complicated by the presence of, and CAS-mediated effects on, SOAEs. As suggested previously (Long et al. 1988a, b; Smurzynski and Probst 1998), SOAEs may mask or otherwise interfere with detection of tones at nearby frequencies, such that the effects of CAS at these frequencies are dominated by a release from masking. CAS-mediated changes in threshold may therefore be determined by both the *primary* effect of MOC-mediated inhibition of the cochlear amplifier and the *secondary* effects of this inhibition on the mechanisms underlying SOAEs and threshold fine structure. These secondary effects can

be as large or larger than the primary effect and may be of the opposite sign when SOAEs are present.

Pathways of the CAS Effect

CAS is predominantly known to elevate behavioral thresholds. The degree of elevation depends on the amplitude, frequency content, and temporal characteristics of the CAS relative to the test tone, though is typically less than 10 dB (e.g., Dirks and Malmquist 1965; Zwislocki et al. 1967). Consistent with previous investigations using moderate-level broadband CAS (e.g., Kawase et al. 2003; see also Smith et al. 2000 for comparable effects in Japanese macaque), we observed CAS-mediated threshold elevations ranging from 2 to 5 dB, but mainly in ears with no measurable SOAEs or prominent threshold fine structure in the frequency range tested. In contrast, we also observed unprecedented threshold improvements (approaching 15 dB) and variability in CAS effects when measured at frequencies associated with SOAEs and/or fine structure. A survey of the contralateral masking literature reveals only a few isolated instances of CAS improving thresholds (by up to 3 dB), primarily when contralateral tones were presented at higher or lower frequencies than the ipsilateral test tone (e.g., Figs. 2 and 3 of Ingham 1959; Fig. 5 in Zwislocki et al. 1967).

Contralateral effects have been attributed to a variety of peripheral and central mechanisms, including interaural crosstalk via air- or bone-conducted sound (Wegel and Lane 1924; Zwislocki 1953), middle ear muscle contraction (Ward 1961; Gjaevenes and Vigran 1967; Youngblood and Martin 1981), MOC inhibition of OHC activity (Kawase et al. 2003; Smith et al. 2000), and binaural interactions occurring more centrally in the auditory system (i.e., “central masking”; e.g., Zwislocki 1972). The moderate level of broadband CAS used in the present study was presumed to primarily elicit MOC activity, as it was insufficient to produce suprathreshold crosstalk and was also below the MEMR threshold for all subjects. While we cannot eliminate the possible influence of binaural interactions at higher auditory centers, the modulation of SOAEs by CAS confirmed MOC activity in our subjects, and the contralateral effects we observed appear to be driven by peripheral modulation of OHC activity and OAE behavior.

Frequency Shifts in Threshold Minima and SOAEs

Variation in CAS-mediated threshold changes across frequency was partially due to a small, upward frequency shift in the threshold fine structure pattern. This shift was anticipated based on previously observed effects of CAS on SOAEs (Mott et al. 1989;

Harrison and Burns 1993; Zhao and Dhar 2010, 2011, 2012) and the close frequency correspondence between threshold minima and SOAEs (e.g., Wilson 1980; Schloth 1983; Zwicker and Schloth 1984). We confirmed that threshold minima occurred very near in frequency to each selected SOAE, with frequency discrepancies typically less than a few Hz (or 0.1 %), both in quiet and with CAS. Correspondingly, CAS-mediated shifts in the frequencies of SOAEs and threshold minima were very similar. Frequency shifts were reliably positive, though typically less than 1 %, and diminished percentage-wise with increasing frequency, consistent with previous reports of CAS effects on SOAEs (see Fig. 3 of Zhao and Dhar 2011).

CAS-mediated frequency shifts can be interpreted within the cochlear resonance framework initially proposed by Kemp (1979a, b). According to this framework, threshold fine structure and SOAEs arise via multiple reflections of OAE energy between the site of OAE generation and the middle ear boundary, leading to resonance at frequencies where the round-trip phase accumulation is an integer number of cycles. The frequencies of threshold minima and SOAEs are therefore determined by the phase delays inherent in the OAE generation mechanism and the reflectance at the stapes. Since the generated OAE occurs at the frequency of stimulation (whether initiated by external sound or internal physiological noise) and may be thought of as a stimulus-frequency OAE (SFOAE), the frequencies of cochlear resonance should be related to SFOAE phase. Consistent with this, SOAEs occur with a frequency spacing that is associated with approximately one cycle of SFOAE phase accumulation (Shera 2003; Bergevin et al. 2012). Changes in SFOAE phase should therefore produce shifts in the frequencies of SOAEs and threshold minima.

Indeed, activation of the MOC system with CAS causes a small *lead* in SFOAE phase (Francis and Guinan 2010), theoretically shifting SOAEs and threshold minima upward in frequency. Phase leads have also been observed in direct measures of basilar membrane motion during electrical stimulation of the MOC system (Cooper and Guinan 2003), although whether these effects are related to changes in SFOAEs is unknown. While we verified absence of MEMR to the CAS, note that alterations of middle ear impedance would produce similar upward frequency shifts (e.g., Kemp 1979a; Wilson and Sutton 1981; Schloth and Zwicker 1983) due to a change in the phase of the stapes reflectance (Shera 2003).

Interestingly, non-MOC-related alterations of cochlear function produce frequency shifts in the opposite direction. SOAE and threshold minima frequencies shift *downward* by 1–2 % following aspirin use (Long and Tubis 1988a, b) and intense noise

exposure (Furst et al. 1992; see also Kemp 1981; Norton et al. 1989 for examination of the effects on SOAEs alone), and by approximately 0.25 % per year of life (Burns 2009). These frequency shifts presumably all arise via phase changes in the SFOAE generating mechanism following reductions in the efficiency of the cochlear amplifier. MOC-mediated effects on the cochlear amplifier therefore differ in this respect from other more dramatic or damaging changes in OHC function.

Interactions Among Cochlear Gain, SOAEs, and Thresholds

The magnitude and direction of CAS-mediated effects on threshold levels and fine structure were largely influenced by the presence of SOAEs and CAS-mediated changes in SOAE level. In the absence of SOAEs, CAS elevated thresholds overall, with larger changes at threshold minima than those at maxima (subject 17FL in Fig. 8C). This is consistent with a reduction in cochlear gain (i.e., an upward shift in the threshold curve) combined with a reduction in the fine structure depth (i.e., an upward shift in thresholds at minima and a downward shift at maxima). The former effect presumably leads to the latter via inhibition of the OAE evoked by the test tone. This inhibition would reduce both constructive and destructive interference caused by intracochlear reflections of the evoked OAE. Similar upward threshold shifts and reductions in fine structure depth have been observed following noise exposure (Furst et al. 1992) and sustained (~3 days) consumption of aspirin (Long and Tubis 1988a, b), which is known to inhibit OHC function (Shehata et al. 1991; Dieler et al. 1991).

The presence of an SOAE typically reversed the aforementioned effects, with CAS improving thresholds, particularly at threshold minima, and increasing fine structure depth. In these cases, the benefit of reducing the SOAE level appeared to dominate the total effect, at least when the level reduction was small. For larger SOAE level reductions, which presumably indicate greater MOC inhibition, the changes in threshold levels and fine structure at nearby frequencies were smaller and/or less consistent (Fig. 7). In one subject (17FL in Fig. 8C), these changes were similar to those observed in the absence of SOAEs (i.e., threshold elevation and reduction in fine structure depth). These cases suggest that when MOC inhibition is strong, any benefit of reducing the SOAE level may be balanced or outweighed by the effects of gain reduction (i.e., elevated thresholds) and diminished intracochlear reflections (i.e., reduced fine structure depth).

Long and Tubis (1988a, b) previously observed this transition from threshold improvements to elevations (at frequencies near those of SOAEs) with increasing aspirin-mediated reductions in cochlear gain. They noted that thresholds were typically improved within the first 8–24 h of aspirin intake, during which SOAEs (but not evoked OAEs) were greatly reduced in amplitude. However, in contrast to the majority of our measurements, thresholds were primarily improved at maxima, with less change at minima, resulting in slight reductions in fine structure depth. This difference may be due to the larger reductions in SOAE levels with aspirin than with CAS, and perhaps the relative number and levels of the SOAEs in the subjects tested. Furst et al. (1992) also observed that noise exposure slightly improved thresholds at frequencies near that of an SOAE (which was reduced in amplitude by ~5 dB) for one subject. However, data from this subject appeared to be an exception to the general trend.

Masking by SOAEs

While SOAEs are associated with local improvements in sensitivity (i.e., threshold minima) and better sensitivity across a wider frequency range (McFadden and Mishra 1993), our results (and those of Long and Tubis 1988a, b) suggest that reducing the amplitude of an SOAE improves signal detection at nearby frequencies. Smurzynski and Probst (1998) demonstrated that the converse is also true, noting in one subject that the ~20-dB growth of an SOAE over the course of a test session was accompanied by threshold elevations at nearby frequencies. Thresholds were elevated by ~10 dB at the associated threshold minimum, with less change observed at the adjacent maxima. These effects essentially mirror those observed in the present study and further suggest that SOAEs cause some form of masking or perceptual interference.

SOAE-related masking may arise via multiple mechanisms. SOAEs are associated with spontaneous basilar membrane vibrations (in guinea pig; Nuttall et al. 2004), as well as elevated spontaneous firing rates in auditory nerve fibers (in chinchilla; Powers et al. 1995). This background activity could modulate responses to external stimuli via mechanical two-tone suppression and neural adaptation or inhibition. These interactions may not be negligible, as SOAE-related vibrations have been estimated to be as much as 30 dB larger than those evoked by tones of equivalent ear canal SPL (Powers et al. 1995). The fact that such vibrations are often not perceived unless perturbed (Zurek 1981; Schloth and Zwicker 1983) suggests that some degree of neural adaptation or inhibition has occurred more centrally. Reducing

SOAE-related background activity would reduce the aforementioned effects and increase the signal-to-noise ratio of neural responses to external sounds, thus improving signal detection.

Threshold levels and fine structure morphology may also be influenced by acoustic interactions between the test tone and the SOAE. A reduction in SOAE amplitude would decrease the stimulus level required to entrain the SOAE (resulting in the perception of a pure tone) and alter the range of stimulus levels over which beating or distortions are perceived, as shown during aspirin consumption (Long et al. 1991). Although these interactions were not a focus of the present study, some subjects reported that perceptions of beating and roughness during the threshold measurements were greatly reduced with CAS. It is unclear whether such interactions aided or hindered threshold detection.

Extension to Evoked OAEs

We focused our measurements on SOAE frequencies so as to reliably locate threshold minima and measure a constant fraction of a threshold fine structure cycle. This facilitated comparison of the measurements across conditions, sessions, and subjects. However, threshold minima are also known to align in frequency with peaks in the spectra of OAEs evoked by low-level transients, even in the absence of measurable SOAEs (Zwicker and Schloth 1984). Long and Tubis (1988a, b) noted that aspirin-induced changes in threshold fine structure tended to parallel changes in the amplitudes of OAEs evoked by low-level transients and tones. These observations are consistent with notion that the fine structure is related to the OAE evoked by the test tone. While more time-consuming than our SOAE recordings, measurement of the CAS-mediated changes in the OAEs evoked at each test frequency may have clarified the interrelationships among threshold fine structure, SOAEs, and evoked OAEs.

Implications for Psychoacoustics

The fine structure of the CAS-mediated effects on pure-tone thresholds may extend to, and therefore complicate, suprathreshold behavioral investigations of MOC activity. Threshold fine structure has been shown to influence measures of temporal integration (Cohen 1982), loudness judgments (Kemp 1979a; Mauermann et al. 2004), psychophysical tuning (Long 1984), and amplitude modulation detection (Zwicker 1986; Heise et al. 2009a, b). Previous assessments of MOC influence on loudness perception (Micheyl et al. 1995a, 1997; Morand-Villeneuve et al. 2002) or psychophysical tuning (Quaranta et al. 2005; Vinay 2008) may therefore have

been influenced by threshold fine structure. Future psychophysical investigations of MOC function may consider using test stimuli with broader frequency content and/or shorter durations (as in Kawase et al. 2000; Jennings and Strickland 2012; Aguilar et al. 2013), since thresholds and other perceptual judgments for these types of stimuli exhibit less fine structure (Cohen 1982; Long 1984; Lee and Long 2012). However, it is not clear if these stimulus types would also reduce the influence of SOAEs, as Smurzynski and Probst (1998) found that thresholds for both long (310 ms) and short (10 ms) test stimuli were elevated by the growth in level of an SOAE at a nearby frequency.

These considerations may be particularly important when investigating relationships between CAS-mediated changes in OAEs and perception. While individuals with large evoked OAEs are ideal for achieving better signal-to-noise ratios in OAE-based MOC assays, they may also be more likely to have threshold fine structure and SOAEs (Moulin et al. 1993; Kulawiec and Orlando 1995; Kapadia and Lutman 1999). Variability in psychoacoustic measures due to MOC modulation of SOAEs or threshold fine structure may be likely in these individuals. As we have illustrated in the present report, the effects of CAS on behavioral measures can vary to a large degree with small changes in test frequency and may be of the opposite sign relative to changes in OAEs.

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Conflict of Interest The authors declare that they have no conflict of interest.

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