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Human medial efferent activity elicited by dynamic versus static contralateral noises

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Abstract

The medial olivocochlear reflex (MOCR) modifies cochlear amplifier function to improve encoding of signals in static noise, but conflicting results have been reported regarding how the MOCR responds to dynamic, temporally-complex noises. The current study utilized three MOCR elicitors with identical spectral content but different temporal properties: broadband noise, amplitude-modulated noise, and speech envelope-modulated noise. MOCR activity was assessed using contralateral inhibition of transient-evoked otoacoustic emissions in 27 normal-hearing young adults. Elicitors were presented contralaterally at two intensities of 50 and 60 dB SPL. Magnitude and growth of contralateral inhibition with increasing elicitor intensity were compared across the three elicitor types. Results revealed that contralateral inhibition was significantly larger at the elicitor intensity of 60 dB SPL than at 50 dB SPL, but there were no significant differences in the magnitude and growth of inhibition across the three elicitors, contrary to hypothesis. These results suggest that the MOCR responds similarly to both static and dynamic noise.

Keywords

medial olivocochlear reflex; auditory efferent system; otoacoustic emissions; contralateral suppression; amplitude modulation; multi-talker babble

Abbreviations

AM, amplitude-modulated; BBN, broadband noise; CAS, contralateral acoustic stimulation; EM, envelope-modulated; MEMR, middle-ear muscle reflex; MOC, medial olivocochlear; MOCR, medial olivocochlear reflex; OAE, otoacoustic emission; pSPL, peak sound pressure level;

34 SSOAE, synchronized spontaneous otoacoustic emission; TEOAE, transient-evoked otoacoustic
35 emission

1. Introduction

The medial olivocochlear (MOC) efferent system modulates cochlear amplifier function through descending fibers that project from the brainstem to the outer hair cells (reviewed in Guinan, 2006). Afferent stimulation of the MOC triggers a reflex (MOC reflex, or MOCR) which improves auditory nerve encoding of transient sounds in background noise by reducing the neural response to the noise (Winslow and Sachs, 1987; Kawase et al., 1993). The MOCR appears to contribute to normal-hearing listeners' ability to understand speech in noisy situations (e.g., Giraud et al., 1997; Mertes et al., 2017). The MOCR is typically assessed non-invasively in humans using transient-evoked otoacoustic emissions (TEOAEs), which are measurable sounds generated in response to brief stimuli that are a byproduct of the cochlear amplification process (Kemp, 1978; Brownell, 1990). When measuring TEOAEs in one ear, presentation of contralateral sound activates the contralateral MOC pathway, decreasing cochlear amplifier gain and reducing TEOAE amplitude (Collet et al., 1990; Berlin et al., 1993). This process is referred to as contralateral inhibition, and larger inhibition is interpreted as a stronger MOCR (Backus and Guinan, 2007).

The MOCR is responsive to a variety of sounds, including pure tones, clicks, tone bursts, and noise (e.g., Veuillet et al., 1991; Berlin et al., 1993; Guinan et al., 2003). The magnitude of contralateral inhibition increases with increasing level and bandwidth of the contralateral stimulus, with static white noise yielding the largest inhibition (Maison et al., 2000; Velenovsky and Glattke, 2002; Guinan et al., 2003; Lilaonitkul and Guinan, 2009). Static white noise therefore has been used as the contralateral stimulus in nearly all studies of contralateral inhibition in humans. Despite the usefulness of using static white noise to study contralateral inhibition in laboratory settings, it is unclear how more dynamic, temporally-complex sounds

activate the MOCR. If the MOCR responds differently to dynamic versus static noises, then measurements of contralateral inhibition using static white noise may not reflect the behavior of the MOCR in the presence of background noises that humans often encounter, such as multi-talker babble.

A small number of studies have examined contralateral inhibition using dynamic contralateral sounds, but results have been equivocal. One group found that amplitude-modulated (AM) sinusoids and AM broadband noise (BBN) yielded larger contralateral inhibition relative to unmodulated sinusoids and unmodulated BBN (Maison et al., 1997; 1999; 2001), consistent with the modulation transfer function measured in individual MOC neurons of the guinea pig (Gummer et al., 1988). However, Boothalingam et al. (2014) found a trend of reduced contralateral inhibition of otoacoustic emissions (OAEs) elicited with single-tone stimuli (stimulus frequency OAEs) when the tones were AM versus unmodulated. No significant differences were seen in contralateral inhibition when elicited by a babble noise relative to white noise (Timpe-Syverson and Decker, 1999; Papsin et al., 2014), but these studies did not report sufficient controls for middle-ear muscle reflex activation which could interfere with the interpretation of results (Goodman et al., 2013) and the click stimulus rate of 50/s may have elicited the ipsilateral MOCR (Boothalingam and Purcell, 2015). A recent paper examined the effect of a variety of contralateral noises on contralateral inhibition (Kalaiah et al., 2017). The noises included BBN, AM noise (4, 50, and 100 Hz modulation frequencies), multi-talker babble (two, four, and six talkers), and environmental (traffic and cafeteria) noises. Results showed that the multi-talker babble and traffic noises elicited significantly lower contralateral inhibition than BBN. The authors concluded that multi-talker babble noise is a less efficient activator of the MOCR than other noises, which could have implications for how the MOCR is activated in real-

world listening situations. However, there were differences in the spectral content of the noises (see their Fig. 2), so it cannot be determined if the differences in MOCR activation were due to differences in the spectral and/or temporal content of the noises.

The primary purpose of the current study was to compare the magnitude of contralateral inhibition elicited by three contralateral noises that varied in their temporal characteristics while holding the spectral content the same. Static BBN and two dynamic noises (AM BBN and BBN modulated by the envelope of multi-talker babble) were utilized. It was hypothesized that BBN would elicit significantly larger contralateral inhibition than the dynamic noises because the lack of low-amplitude dips in the static noise would ensure sustained activation of the MOCR (Boothalingam et al., 2014). The growth of contralateral inhibition for the three noise elicitors was also explored to determine if the MOCR responds differentially across elicitor intensity level depending upon the temporal characteristics of the elicitor.

2. Material and methods

2.1. Participants

A total of 27 participants (20 females) participated. Participant ages ranged from 18 to 40 years [mean = 23.5 years, standard deviation (SD) = 5.9]. Screening procedures included a case history and audiologic screening. Eligible participants were required to have a self-reported negative history of the following: hearing difficulties, significant noise exposure within the past 6 months, tinnitus of a severe and/or bothersome nature, use of ototoxic medication, vertigo, and chronic middle ear pathology. Participants were also required to be right handed to avoid confounds of handedness effects on contralateral inhibition (Khalfa et al., 1998).

Audiologic inclusion criteria consisted of the following: an unremarkable otoscopic examination bilaterally, normal 226-Hz tympanograms bilaterally (tympanometric peak pressure between -100 to +50 daPa, static acoustic admittance between 0.2 to 1.8 mmho, and equivalent ear canal volume from 0.6 to 2.5 cc), pure-tone air-conduction thresholds ≤20 dB HL at octave frequencies from 250 to 8000 Hz bilaterally, and measurable TEOAEs in the right ear. The TEOAE screening measurement consisted of collecting 1250 sweeps in response to 40.96-μs clicks presented at 65 dB peak sound pressure level (pSPL) at a rate of 19.53/s using equipment described in Sec. 2.2. Mean TEOAE waveforms were bandpass filtered from 1000 to 2000 Hz. Participants passed the TEOAE screening if the time-domain signal-to-noise ratio (SNR) was >6 dB and the whole-waveform reproducibility (Kemp et al., 1990) was >70%.

The study protocol was approved by the Institutional Review Board of the University of Illinois at Urbana-Champaign. Written informed consent was obtained by all participants prior to their enrollment in the study. All participants received monetary compensation for their participation.

2.2. Equipment

Participants were seated in a comfortable recliner inside a 200 sq. ft. single-walled sound-treated booth with 8-in thick walls (Tracoustics, Inc., Austin, TX). To further reduce external noise from entering the sound booth, the experimenters were situated in a separate room with the door closed. The experimenters monitored participants during the experiment via a camcorder and intercom.

Audiometric screenings were conducted using an AudioStar Pro audiometer (Grason-Stadler, Inc., Eden Prarie, MN) and a Titan tympanometer (Interacoustics, Middelfart, Denmark).

Contralateral inhibition testing was conducted using a WS-4 workstation [Tucker-Davis Technologies (TDT), Alachua, FL] and an RZ6 auditory processor (TDT) running custom software written in MATLAB (ver. R2017a, The Mathworks, Inc., Natick, MA) and RPvdsEx (TDT). Stimuli were routed from the RZ6 to two resistors (1/8 W, 22 Ω) that were placed in series with a pair of ER-2 insert earphones (Etymōtic Research, Elk Grove Village, IL). The acoustic tubing of the right insert earphone was connected to an ER-10B+ probe microphone system (Etymōtic Research) with the preamplifier gain set to +40 dB. The signal recorded by the microphone was routed to the input of the RZ6, sampled at 24414.06 Hz (the default sampling rate of the processor), and streamed to the workstation hard disk.

Offline analyses of TEOAE waveforms were performed using a combination of custom MATLAB code and the MATLAB Signal Processing Toolbox (ver. 11.1, The Mathworks, Inc.). Statistical analyses were conducted using SPSS Statistics (version 24.0.0.0, IBM Corp., Armonk, NY).

2.3. Contralateral inhibition measurement

Stimulus and recording parameters were adapted from those described in Mertes et al. (2017). Contralateral inhibition measurement consisted of obtaining TEOAEs with and without the three contralateral elicitors described in this section. TEOAEs were elicited using clicks generated by the RZ6 processor at the default sampling rate of 24414.06 Hz. Click stimuli were 40.96 μs in duration and were presented at a level of 65 dB pSPL and at a rate of 19.53/s. The stimulus level was selected to ensure robust elicitation of TEOAEs in all participants (Mertes et al., 2017), while the rate was selected to reduce potential elicitation of both the ipsilateral MOCR and the middle-ear muscle reflex (MEMR) by the click stimuli (Boothalingam and Purcell,

2015). The activation of either of these reflexes can confound the interpretation of the contralateral inhibition results and are thus desirable to avoid (Guinan et al., 2003; Boothalingam and Purcell, 2015).

Three noise stimuli served as contralateral elicitors of the MOCR (referred to hereafter as *elicitor types*): 1) broadband noise (*BBN*) consisting of Gaussian noise generated by the RZ6 processor with a nominal bandwidth of 0 to 12207 Hz; 2) amplitude-modulated (*AM*) BBN, consisting of the BBN from elicitor 1 that was amplitude-modulated at a rate of 100 Hz and at a modulation depth of 100%; 3) envelope-modulated (*EM*) BBN, consisting of the BBN from elicitor 1 that was modulated by the envelope of a four-talker babble stimulus (Lilly et al., 2011), where the envelope was obtained by convolving the absolute value of the babble stimulus with a 7.2-ms rectangular window (Brungart et al., 2001). The AM elicitor was utilized to determine the replicability of the results of Maison et al. (1999). EM noise was utilized to determine if the MOCR is responsive to the aperiodic amplitude fluctuations that are present in multi-talker babble. The first 1000 ms of each elicitor waveform are shown in Figure 1. Waveforms were ramped on and off with 50-ms cosine-squared ramps. Elicitor waveforms were scaled to have an equal root-mean-square (RMS) amplitude and the SPLs were calibrated in a 2-cc coupler.

Contralateral inhibition was assessed by interleaving measurements of TEOAEs without and with contralateral acoustic stimulation (referred to hereafter as *CAS*- and *CAS*+, respectively). A single interleave consisted of 8 s in CAS- (clicks only), followed by 500 ms of elicitor presentation to allow for the onset of the MOCR (Backus and Guinan, 2006), followed by 8 s in CAS+ (clicks and elicitor), and finally 500 ms of silence to allow for the offset of the MOCR prior to the next presentation of CAS- (Backus and Guinan, 2006). Each elicitor waveform was 4.8 min in duration. To avoid presenting frozen noise, each interleave in CAS+

involved presenting a random 8-s segment drawn from the total elicitor waveform. The waveforms were then ramped on and off with a 10-ms cosine-squared window. A total of 1250 sweeps in each of the CAS- and CAS+ conditions (i.e., eight interleaves of CAS- and CAS+ conditions) were obtained for a single measurement of contralateral inhibition. Recorded waveforms were high pass filtered with a second-order Butterworth filter with a cutoff frequency of 500 Hz via the RPvdsEx software, then streamed to disk for offline analysis.

For each contralateral noise stimulus, a measurement of contralateral inhibition was obtained by presenting the noise at 50 or 60 dB SPL (A-weighted RMS) (hereafter referred to as *elicitor intensity*). Therefore, there were a total of six conditions (3 elicitor types × 2 elicitor intensities) for each participant. The presentation order of conditions was randomized for each participant.[1] Prior to the recording at each condition, the click stimulus levels were calibrated in-situ and were adjusted until the pSPL of the click was within ±0.25 dB of the target level.

Participants were instructed to remain as still and quiet as possible during the contralateral inhibition measurements. Participants watched a closed-captioned silent video of their choice on an iPad Air 2 tablet (Apple, Cupertino, CA). After each measurement, there was a brief intermission while the experimenter prepared the software for the next recording. Participants were provided with a short break between measurements as needed. The earphones were kept inserted between measurements.

2.4. MEMR analysis

Prior to analyzing the contralateral inhibition results, it was critical to assess the presence of MEMR activation. We implemented a check for the presence of MEMR based on recent reports (Abdala et al., 2013; Boothalingam and Purcell, 2015; Mertes and Leek, 2016), where

196 changes in stimulus amplitude measured in the ear canal were compared between CAS- and
197 CAS+. The rationale for this method is that activation of the MEMR can alter middle ear
198 impedance and thus alter the stimulus amplitude measured in the ear canal. The stimulus
199 waveforms recorded in the ear canal were time-windowed to isolate the stimulus peak. Probable
200 activation of the MEMR was considered present when the mean peak amplitude in CAS+ was
201 ≥0.12 dB larger relative to CAS-. The presence of MEMR was assessed in all elicitor type ×
202 elicitor intensity conditions. However, no participants demonstrated probable MEMR activation.
203
204 *2.5. Contralateral inhibition analysis*
205 For each contralateral inhibition measurement, the waveforms were split into two
206 matrices comprising TEOAEs obtained in CAS- and CAS+. Both matrices were reshaped into
207 1250 sweeps, where time zero was set to the time location corresponding to the stimulus peak.
208 TEOAE waveforms were time windowed from 8 to 18 ms (Hood et al., 1996) and ramped on and
209 off with 1-ms cosine-squared ramps so that the waveforms were at full amplitude from 8 to
210 18 ms. Waveforms were then bandpass filtered with a Hann window-based filter (passband =
211 891 to 2245 Hz, filter order = 128). Artifacts were rejected post hoc by excluding any sweep
212 having an RMS amplitude that fall outside 1.5 times the interquartile range of the distribution of
213 RMS amplitudes across all sweeps (Goodman et al., 2009).
214 Quantification of contralateral inhibition was performed using methods based on Mertes
215 and Leek (2016). Estimates of the TEOAE signal and noise floor amplitudes were first computed
216 by putting odd- and even-numbered sweeps into sub-buffers *A* and *B*, respectively. The TEOAE
217 signal waveform was obtained as $\frac{(A+B)}{2}$ and the TEOAE noise floor waveform was computed as
218 $\frac{(A-B)}{2}$ (Prieve et al., 1993). A mean signal waveform and mean noise floor waveform were

obtained for both CAS- and CAS+. When measured in an IEC711 coupler, the RMS SNR was <6 dB, indicating sufficiently low system distortion. Figure 2 shows an example of mean TEOAE waveforms in CAS- and CAS+ for one representative participant. The SNR of the mean waveform in CAS- was required to be >6 dB to be included in the contralateral inhibition analysis. Contralateral inhibition was computed as the difference in RMS amplitude between the mean TEOAE waveforms in CAS+ and CAS-, expressed in decibels. Positive values indicated that TEOAE magnitude decreased in CAS+, which was the expected effect. Larger positive values were interpreted as stronger MOCR activity (Backus and Guinan, 2007).

We also examined contralateral inhibition within 2-ms time windows to examine differences in contralateral inhibition across different times among the three elicitor types and two elicitor intensities. Due to the frequency dispersion of TEOAEs across time, later analysis windows represent MOCR effects on lower frequencies (Berlin et al., 1993). Velenovsky and Glattke (2002) found that when comparing different contralateral MOCR elicitors, significant differences were seen in the amount of contralateral inhibition across these time windows. Therefore, it was of interest to determine if a similar result would be seen across the different noise elicitors used in the current study. Contralateral inhibition was calculated in the same way as described above in Sec. 2.5, except rather than computing across the duration 8 to 18 ms, five non-overlapping analysis windows were utilized: 8–10, 10–12, 12–14, 14–16, and 16–18 ms.

3. Results

3.1 Magnitude of contralateral inhibition

TEOAE signal and noise floor amplitudes across elicitor type × elicitor intensity conditions are shown in Fig. 3. As expected, TEOAE amplitudes in CAS- appeared stable and

TEOAE amplitudes decreased in CAS+ across all conditions. Additionally, noise floors appeared stable across conditions and were comparable between CAS- and CAS+. Mean SNRs for the 50 dB SPL elicitor intensity were 19.34 dB for CAS- and 17.30 dB for CAS+ (collapsed across elicitor). Mean SNRs for the 60 dB SPL elicitor intensity were 19.38 dB for CAS- and 15.59 dB for CAS+ (collapsed across elicitor). TEOAE signal amplitudes were not normally distributed at all elicitor type × elicitor intensity conditions as assessed by Shapiro-Wilk tests of normality ($p < 0.05$), therefore the mean TEOAE signal amplitudes across conditions were not analyzed with repeated measures analyses of variance (ANOVA).

However, the primary outcome of interest was contralateral inhibition (i.e., the difference in TEOAE amplitude between CAS- and CAS+). Mean contralateral inhibition values are shown in Fig. 4. A two-way repeated measures ANOVA was run to determine the effect of the factors of elicitor type (BBN, AM, and EM) and elicitor intensity (50 and 60 dB SPL) on contralateral inhibition. Outlier detection was utilized by examining the studentized residuals, which are residuals divided by an estimate of the standard error. No outliers were present, as evidenced by studentized residuals that did not exceed ±3 standard deviations. Contralateral inhibition was normally distributed as assessed by a Shapiro-Wilk test of normality on the studentized residuals ($p > 0.05$). Mauchly's test of sphericity indicated that the assumption of sphericity was met for the interaction between elicitor type and elicitor intensity, the main effect of elicitor type, and the main effect of elicitor intensity ($p > 0.05$ in all cases). There was no significant interaction between elicitor type and elicitor intensity, $F(2,52) = 1.560$, $p = 0.220.$, $\chi^2(2) = 3.155$, $p = 0.207$. The main effect of elicitor type was not statistically significant, $F(2,52) = 2.940$, $p = 0.062$. The main effect of elicitor intensity showed that there was a statistically significant difference in contralateral inhibition between elicitor intensities, $F(1,26) = 34.925$, $p < 0.0005$, partial η^2 =

0.573. Post hoc analysis revealed that contralateral inhibition significantly increased from an elicitor intensity of 50 dB SPL to 60 dB SPL (1.477 dB, 95% CI = 0.963 to 1.990, $p < 0.0005$).

Mean results of the analysis in 2-ms time windows are plotted in Fig. 5. The left and right panels display the results obtained for elicitor intensities of 50 and 60 dB SPL, respectively. Two outliers were present, as evidenced by studentized residuals that exceeded +3 standard deviations. Additionally, contralateral inhibition was not normally distributed at all analysis window × elicitor type × elicitor intensity conditions, as assessed by Shapiro-Wilk tests of normality on the studentized residuals ($p < 0.05$). Therefore, a three-way repeated measures ANOVA was not performed. Rather, the data were analyzed qualitatively.

At a given analysis window, mean contralateral inhibition was larger for an elicitor intensity of 60 dB SPL compared to 50 dB SPL, which was expected given the results shown in Fig. 4. At both elicitor intensities, contralateral inhibition was smallest at 8–10 ms. For a given elicitor type, fluctuations in contralateral inhibition can be seen with increasing analysis window. Across analysis windows, differences in contralateral inhibition among the three elicitor types can be seen – no clear pattern emerged for an elicitor intensity of 50 dB SPL but BBN tended to exhibit larger contralateral inhibition relative to the other elicitor types at 60 dB SPL.

3.2 Inhibition versus enhancement of TEOAE amplitude

It was also of interest to examine the distribution of contralateral inhibition values at each elicitor type × elicitor intensity condition. Box and whisker plots of contralateral inhibition are displayed in Fig. 6. The majority of contralateral inhibition values were positive, indicating that TEOAE amplitude decreased in CAS+ as expected. However, there were instances of negative inhibition values at each elicitor type × elicitor intensity condition (ranging from 6 to 7 instances

at 50 dB SPL and from 3 to 4 instances at 60 dB SPL). These enhancements in TEOAE amplitude could not be explained by MEMR activation.

We examined the potential contribution of synchronized spontaneous OAEs (SSOAEs) to these enhancements. SSOAEs are outer hair cell responses that become entrained to click stimuli and persist for longer than TEOAEs (Prieve and Falter, 1995). Participants with SSOAEs may exhibit phase cancellations between SSOAEs and TEOAEs in the absence of MOCR activation. If the MOCR differentially inhibited SSOAEs versus TEOAEs, there may be an increase in the measured TEOAE amplitude (S. Boothalingam, personal communication). Such an effect would be similar to the well-established differential impact of MOCR activation on the distortion versus reflection components of distortion-product otoacoustic emissions, which can result in increases in OAE amplitude when the MOCR is activated (e.g., Abdala et al., 2009).

SSOAEs were extracted using the same methods described in Sec. 2.5 but using a time window from 36 to 44 ms post-stimulus onset, where no TEOAEs were expected to occur. To detect the presence of SSOAEs, a 1024-point FFT was computed on the mean waveform in the SSOAE window and was compared to the FFT computed on the mean waveform in the TEOAE window (8 to 18 ms). SSOAEs were considered present if the SNR in the SSOAE window was >6 dB. Two case examples of participants with SSOAEs are shown in Fig. 7. Results are shown for AM noise presented at 50 dB SPL, in which 7 participants showed enhancements with CAS+. The top row shows results from a participant with enhancements and the bottom row shows results from a participant with inhibition. The participant shown in the top row demonstrated enhancements in both TEOAE and SSOAE amplitude in CAS+. Visual inspection of data showed that of the seven participants demonstrating enhancements in TEOAE amplitude, four of them also demonstrated SSOAEs that also were enhanced with CAS+ (the remaining three did

not have SSOAEs). The participant in the bottom row of Fig. 7 demonstrated inhibition in both TEOAE and SSOAE amplitudes in CAS+. The remaining 11 participants with SSOAEs and inhibition also demonstrated this same trend. Results suggest that SSOAEs are not always associated with enhancements.

3.3 Growth of contralateral inhibition

The growth in contralateral inhibition across elicitor intensities of 50 to 60 dB SPL was compared for the three elicitors. For each participant, the slope for each elicitor was computed in dB/dB as the difference in contralateral inhibition at 60 dB SPL minus contralateral inhibition at 50 dB SPL, divided by 10 dB. Box and whisker plots of growth across elicitor are shown in Fig. 8. Median growth of contralateral inhibition with increasing elicitor intensity was 0.11, 0.13, and 0.12 dB/dB for BBN, AM, and EM, respectively. At each elicitor type, three to four growth values were negative, indicating that contralateral inhibition decreased as elicitor intensity increased.

It was of interest to compare the growth in contralateral inhibition magnitude across the two elicitor intensities; however, growth did not meet the assumptions of a one-way repeated measures ANOVA. One outlier was present for AM growth, as evidenced by a studentized residual that exceeded +3 standard deviations. Additionally, BBN growth was not normally distributed as assessed by a Shapiro-Wilk test of normality on the studentized residuals ($p < 0.05$). Therefore, a Friedman nonparametric test was performed to compare median growth across elicitors. The results revealed that there was no statistically significant difference in growth across the three elicitor types, $\chi^2(2) = 3.630$, $p = 0.163$.

4. Discussion

4.1 Impact of static versus dynamic noises on contralateral inhibition

The purpose of the current study was to determine the impact of temporal characteristics of noise elicitors on the magnitude and growth of contralateral inhibition of TEOAEs. The noise elicitors all had the same long-term average spectrum and RMS amplitude to isolate the temporal effects of 100-Hz amplitude modulation and the envelope of a four-talker babble noise. Contrary to our hypothesis that BBN would elicit larger inhibition, there was no significant difference in the magnitude of contralateral inhibition across elicitors at 50 or 60 dB SPL. Additionally, there was no significant difference in the growth of inhibition across elicitors. The only statistically significant finding was that the magnitude of inhibition increased from 50 to 60 dB SPL, which was expected and has been demonstrated previously for BBN (Veuillet et al., 1991; Hood et al., 1996).

Our results are inconsistent with the findings of Maison and colleagues, who systematically investigated the impact of the frequency and depth of amplitude modulation of BBN (Maison et al., 1999; 2001) presented contralaterally during measurement of OAEs. Their work found that a modulation frequency of 100 Hz and modulation depth of 100% evoked the largest inhibition relative to other modulated and unmodulated stimuli. It is also of note that Maison et al. (1997) found similar results when using amplitude-modulated sinusoids as contralateral elicitors. The authors discussed that the results were consistent with physiologic data that includes the modulation transfer function of single MOC neuron fibers (Gummer et al., 1988) and encoding of amplitude modulation by chopper cells in the ventral cochlear nucleus (Frisina et al., 1990).

More recent work, including the current study, suggests that MOCR activation is similar whether the stimuli are unmodulated or amplitude modulated. Boothalingam et al. (2014) found no statistically significant difference in contralateral inhibition of stimulus frequency OAEs and tone-burst OAEs for BBN that was either unmodulated or amplitude modulated at 100 Hz and presented at 60 dB SPL. The authors observed a trend of decreased inhibition in response to AM stimuli relative to unmodulated stimuli and speculated that the silent periods or "dips" in the AM stimuli may reduce sustained activation of the MOCR given its onset time course of approximately 275 ms (Backus and Guinan, 2006). Our results showed a similar trend (see Fig. 4). Our random selection of 8-s segments of the noise waveforms upon each presentation, combined with a click rate of 19.53/s that would not synchronize with the AM or EM noise, likely caused some TEOAEs to be recorded in the presence of modulations dips and some in the presence of modulation peaks, which may have\ reduced the contralateral inhibition of TEOAEs in response to AM and EM noise, relative to BBN. However, it is important to note that Boothalingam et al. (2014) found no significant difference in contralateral inhibition when the modulation frequency of the AM noise elicitor was synchronized versus unsynchronized to the click presentation rate. The results of Kalaiah et al. (2017) also demonstrated no significant difference in inhibition for unmodulated BBN and BBN that was amplitude-modulated at 4, 50, and 100 Hz when presented at 60 dB SPL.

It is unclear why Maison and colleagues consistently found increased inhibition for 100-Hz AM elicitors whereas more recent studies did not. All studies utilized low OAE-eliciting stimulus levels (ranging from 55 to 65 dB peak SPL), so cochlear amplifier gain was presumably adequate to allow for an MOCR-induced change in gain (Hood et al., 1996; Guinan, 2006). Boothalingam et al. (2014) verified that the OAE-eliciting stimulus rate used by Maison's group

did not explain the increased inhibition for 100-Hz AM. All studies presented the contralateral noises at 60 dB SPL, which likely ensured that the MEMR was not activated and allowed for across-study comparisons. We added the 50 dB SPL condition to see if the difference in inhibition across elicitor type was dependent upon elicitor intensity, but we found no significant elicitor type × elicitor intensity interaction. Additionally, we found that contralateral inhibition grew by 0.11 to 0.13 dB per 1-dB increase in elicitor intensity, which is broadly consistent with previous work on BBN (Veuillet et al., 1991; Hood et al., 1996). It may be possible that subtle differences related to the participants, OAE measurement, and/or OAE analysis may have contributed to the discrepant findings regarding the impact of modulated noises on the MOCR.

4.2 Implications for listening in noise

Our results, combined with those of Boothalingam et al. (2014) and Kalaiah et al. (2017), may suggest a real-world benefit of the MOCR for listening in background noise. MOCR function is associated with reduced neural adaptation in response to BBN (Kawase et al., 1993) and with the ability to understand speech in the presence of static BBN (Giraud et al., 1997; Kumar and Vanaja, 2004; Mertes et al., 2017). If modulated noises encountered in typical listening situations (e.g., multi-talker babble) also activate the MOCR, then benefits for speech-in-noise understanding may be conferred. However, experimental examination of such benefits would need to consider the confounding (although beneficial) effect of listening in the "dips" of modulated noises, which have been shown to improve speech-in-noise abilities relative to unmodulated noises (e.g., Festen and Plomp, 1990). Additionally, the contralateral inhibition reported in the current study and related studies only represents the overall MOCR effect computed across tens of seconds or more.

When examined in 2-ms portions, contralateral inhibition tended to be smaller from 8–10 ms relative to later time windows for all noise elicitors and noise intensities (Fig. 8). The difference in contralateral inhibition across the elicitor types appeared to be minimal. Velenovsky and Glattke (2002) found a considerable difference in contralateral inhibition across elicitor types using a similar time analysis method, but the elicitors varied in their bandwidth, whereas the bandwidth of elicitor types in the current study were identical. The finding of less contralateral inhibition from 8–10 ms is consistent with a recent study which also showed a plateau in contralateral inhibition after the 8–10 ms window (Kalaiah et al., 2017). It should be noted that we did not analyze the time course of the MOCR in a systematic way, so we may have missed important differences in how the MOCR is activated by the elicitors across shorter time periods relevant to perceiving individual speech sounds during running speech (Backus and Guinan, 2006). Measuring OAEs that are elicited with continuous stimuli, such as stimulus-frequency and distortion-product OAEs, may be preferable to measuring TEOAEs for examining such changes (e.g., Backus and Guinan, 2006; Harrison et al., 2008).

As noted in Sec. 4.1, the noise elicitors in the current study had the same long-term spectrum. Kalaiah et al. (2017) included actual multi-talker babble stimuli (2, 4, and 6 talkers) as contralateral elicitors, which substantially reduced the high-frequency energy relative to the BBN. They found that the multi-talker babble only elicited mean inhibition values of ≤0.5 dB, significantly lower than their mean inhibition of 1.5 dB for BBN. This may suggest that multi-talker babble is a weak activator of the MOCR due to its low pass nature. However, multi-talker babble may contain discernible speech that can draw the listener's attention and thus increase or decrease MOCR activation (reviewed in Meric and Collet, 1994). Such an attentional effect might be minimized by utilizing time-reversed multi-talker babble or through explicit

425 instructions to participants regarding how they should direct their attention during the
426 contralateral inhibition measurements.
427
428 *4.3 Inhibition versus enhancement of TEOAE amplitude*
429 Figure 6 demonstrates that a minority of participants exhibited enhancement, rather than
430 inhibition, of TEOAE amplitude with MOCR activation. Although these enhancements have
431 been found in other OAE-based studies of the MOCR (Hood et al., 1996; Goodman et al., 2013),
432 the enhancements are inconsistent with physiologic work demonstrating that the MOCR
433 decreases cochlear amplifier gain (Murugasu and Russell, 1996; Cooper and Guinan, 2006). One
434 potential cause of these enhancements is activation of the MEMR, which can decrease middle
435 ear impedance above 1 kHz and may serve to increase TEOAE amplitudes (Boothalingam and
436 Purcell, 2015). We found no evidence of MEMR activation as assessed by examining changes in
437 the stimulus amplitude measured in the ear canal, although we cannot rule out subtle impedance
438 changes not detected by our methodology. We also qualitatively investigated the contribution of
439 SSOAEs to these enhancements (Fig. 7). As described in Sec. 3.2, the MOCR may differentially
440 impact SSOAEs and TEOAEs and result in amplitude enhancements. All participants who
441 exhibited enhancements had SSOAEs in the 1000 to 2000 Hz region. However, some
442 participants who exhibited inhibition also had SSOAEs. It appears that SSOAEs may be
443 necessary, but not sufficient, for MOCR enhancements. Recent in work in guinea pigs has found
444 that MOCR enhancements in OAE amplitude may be caused by the MOCR increasing cochlear
445 roughness (and thus increased levels of reflection-source OAEs), at least when the MOCR is
446 elicited by electrical shocks (Berezina-Greene and Guinan, 2017). More work is needed to

447 understand the cause of MOCR enhancements in humans and their relevance to assessing MOCR
448 activity.
449
450 *4.4 Future directions*
451 More work is needed to better understand how the MOCR responds to a variety of noise
452 sources that vary in both spectral and temporal properties, and how the resulting efferent
453 response influences auditory perception. The methodology used in the current study was limited
454 to a contralateral presentation of the MOCR elicitors. Forward masking paradigms allow for
455 bilateral presentation of MOCR elicitors (Berlin et al., 1995) and would therefore provide insight
456 into the MOCR as it would behave in real-world binaural listening, although it does not allow for
457 an examination of simultaneous masking. We examined the change in TEOAE amplitude to
458 compare with previous studies but characterizing the change in both TEOAE amplitude and
459 phase may reveal subtle differences in how the MOCR responds to different temporal and
460 spectral characteristics of stimuli. Additionally, we only used one stimulus level to evoke
461 TEOAEs; it is possible that use of lower stimulus levels may provide more sensitive
462 measurement of contralateral inhibition that could reveal larger differences in MOCR activation
463 across elicitors. Using a more stringent SNR criterion (e.g., 20 dB; Goodman et al., 2013) would
464 reduce the impact of physiologic and instrumentation noise on measurements of contralateral
465 inhibition. However, this would reduce the number of participants included in the current study
466 and thus reduce statistical power. SNR could be increased by increasing the number of sweeps.
467 However, there may be a risk of introducing variability in attentional state between elicitor type
468 × elicitor intensity conditions by increasing the duration of measurements. Finally, experiments
469 that allow for concurrent measurements of the MOCR during perceptual tasks (e.g., Zhao et al.,

2014) will serve to bridge the gap between physiologic measurements of MOCR activity and the functional relevance of the MOCR when listening to speech in background noise.

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615 **Figure captions**

616 **Fig. 1.** Waveforms of the three contralateral elicitors. Each panel displays the first 1000 ms.

617

618 **Fig. 2.** Example mean TEOAE waveforms obtained in CAS- and CAS+. Data are shown for a
619 representative participant in response to BBN at 60 dB SPL. Time is shown relative to the
620 stimulus peak location. TEOAE RMS amplitude decreased in CAS+ as expected.

621

622 **Fig. 3.** Mean TEOAE signal and noise floor amplitudes across elicitor type × elicitor intensity
623 conditions. The vertical dashed line separates results for intensities of 50 dB SPL (left) and 60
624 dB SPL (right). Error bars represent +1 SEM.

625

626 **Fig. 4.** Mean contralateral inhibition across elicitor type × elicitor intensity conditions. Error bars
627 represent +1 SEM.

628

629 **Fig. 5.** Analysis of contralateral inhibition in 2-ms time windows. The left and right panels
630 represent results obtained at elicitor intensities of 50 and 60 dB SPL, respectively. Bars represent
631 mean values. Error bars represent +1 SEM.

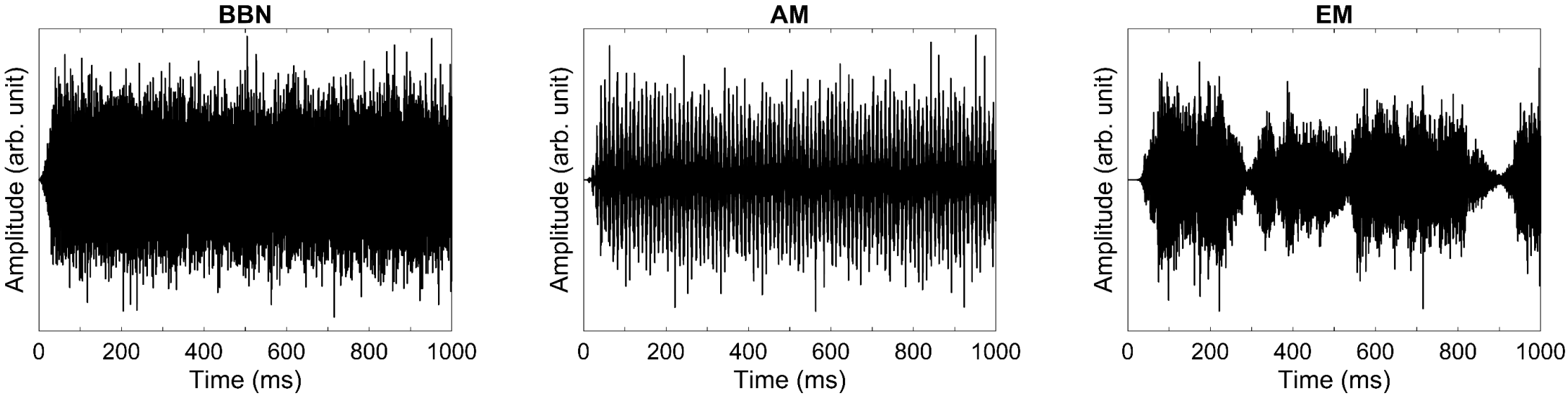
632

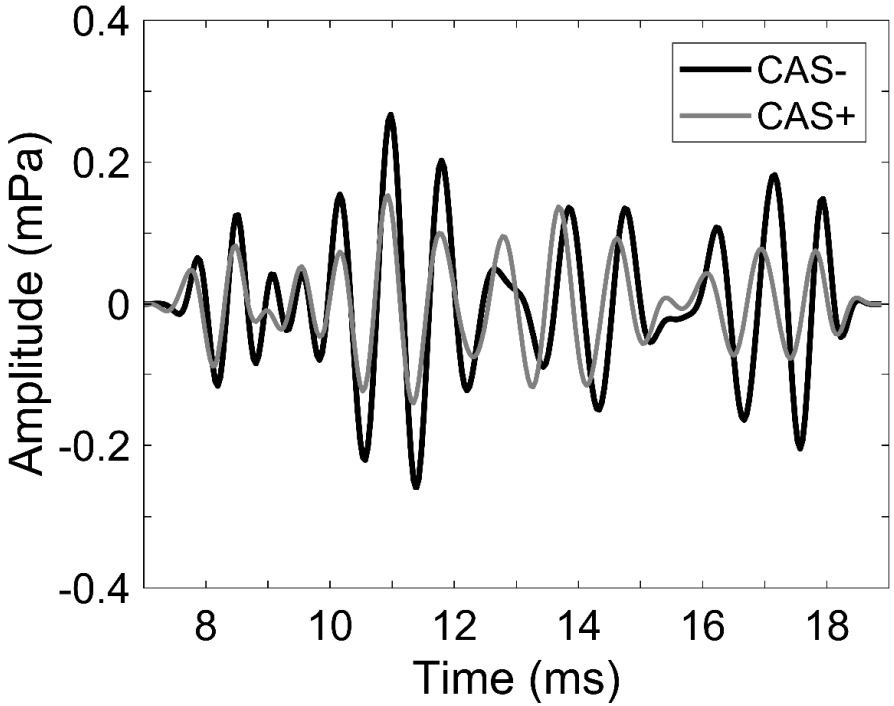
633 **Fig. 6.** Distribution of contralateral inhibition at each elicitor type × elicitor intensity condition.
634 Boxes encompass the middle 50% of the data. Thick horizontal lines within each box are the
635 medians. The whiskers extend to the largest and smallest values not considered outliers. Crosses
636 represent outliers. The gray horizontal line is used to separate inhibition (positive values) from

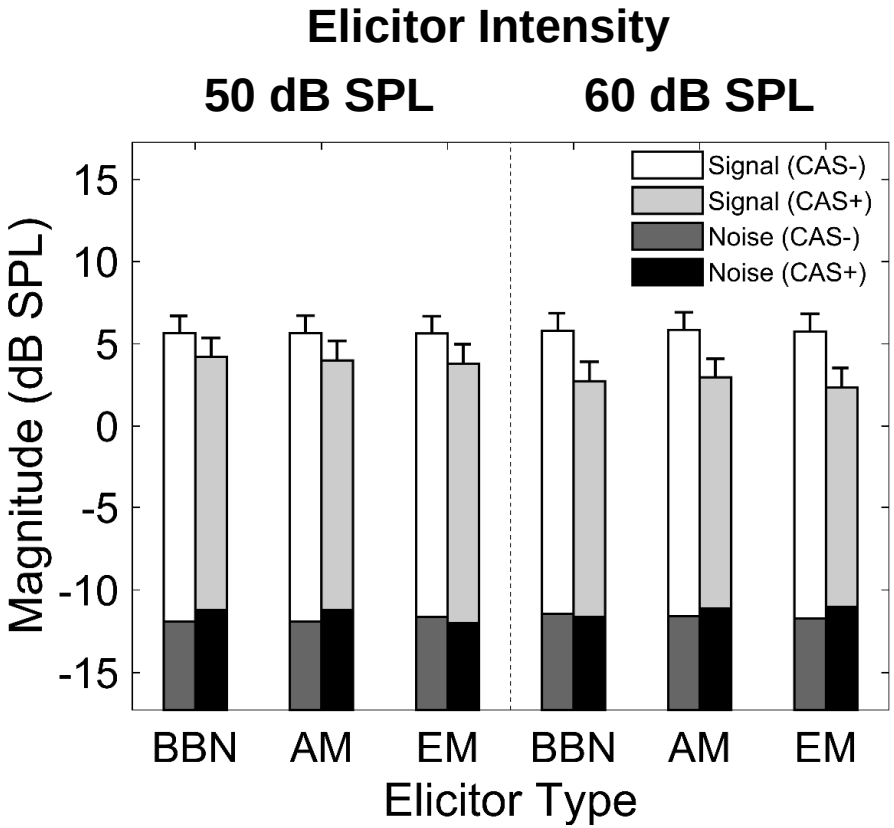
637 enhancement (negative values). The vertical dashed line separates results for elicitor intensities
638 of 50 dB SPL (left) and 60 dB SPL (right).
639
640 **Fig. 7.** Comparison of a participant with contralateral enhancement (top row) versus contralateral
641 inhibition (bottom row). Panels on the left show FFTs computed on the analysis window from 8
642 to 18 ms. Panels on the right show FFTs computed on the analysis window from 34 to 42 ms.
643 Thin dashed lines represent the recording noise floors in the CAS- (black) and CAS+ (gray)
644 conditions. Results were obtained for AM noise presented at 50 dB SPL.
645
646 **Fig. 8.** Distribution of growth in contralateral inhibition with increasing elicitor intensity. Boxes
647 encompass the middle 50% of the data. Thick horizontal lines within each box are the medians.
648 The whiskers extend to the largest and smallest values not considered outliers. Crosses represent
649 outliers. The gray horizontal line is used to visually separate positive from negative growth.

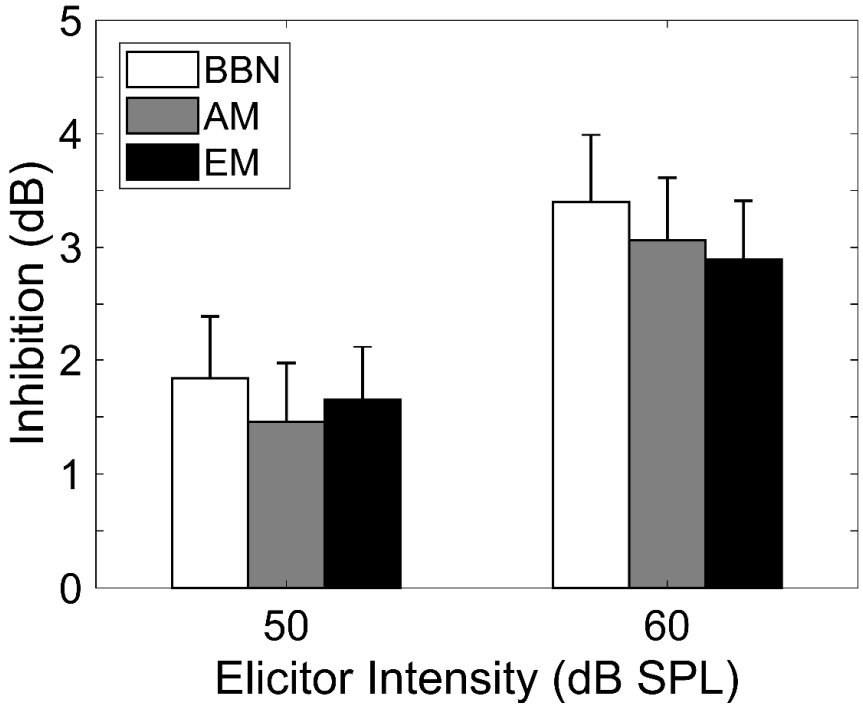
650 **Footnotes**

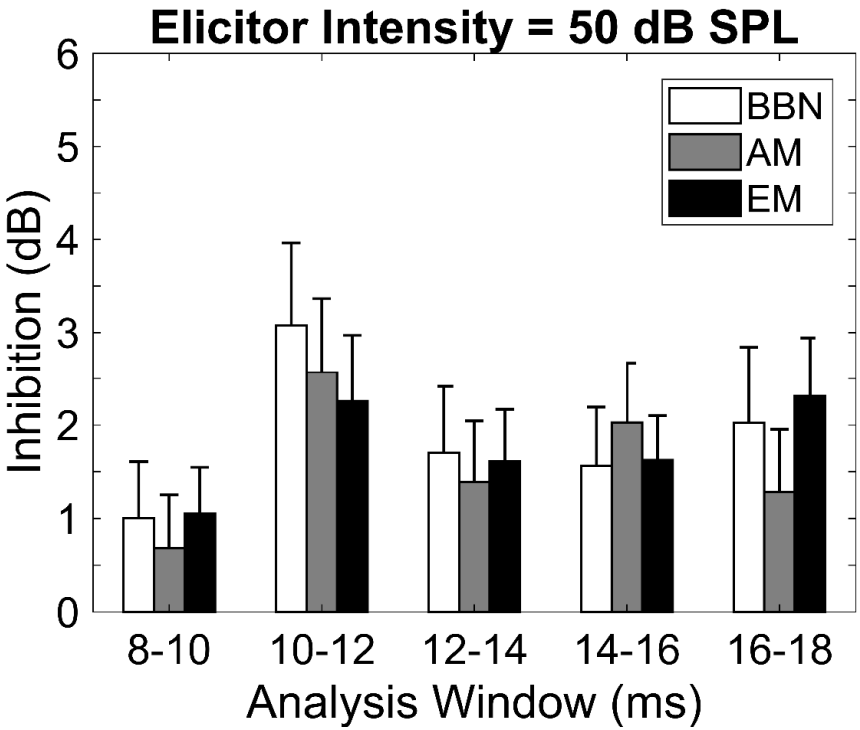
651 [1] Due to a programming error in the randomization sequence, the first two participants were
652 inadvertently presented with the same order of contralateral noise conditions (elicitor ×
653 intensity). This error was subsequently corrected and did not affect the remaining participants.

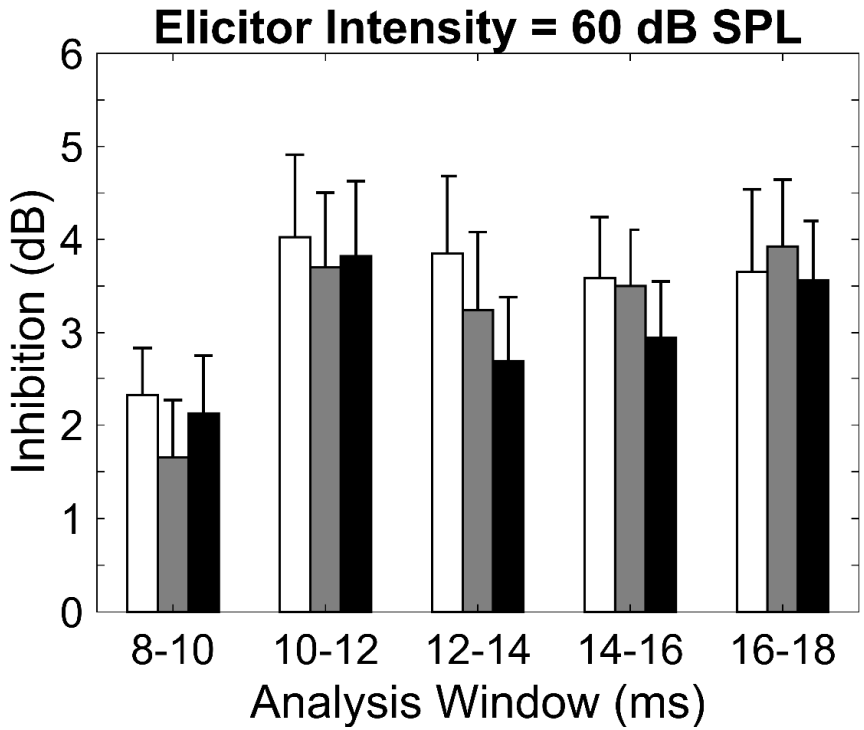

BBN
AM
EM
Amplitude (arb. unit)
Time (ms)
0
200
400
600
800
1000

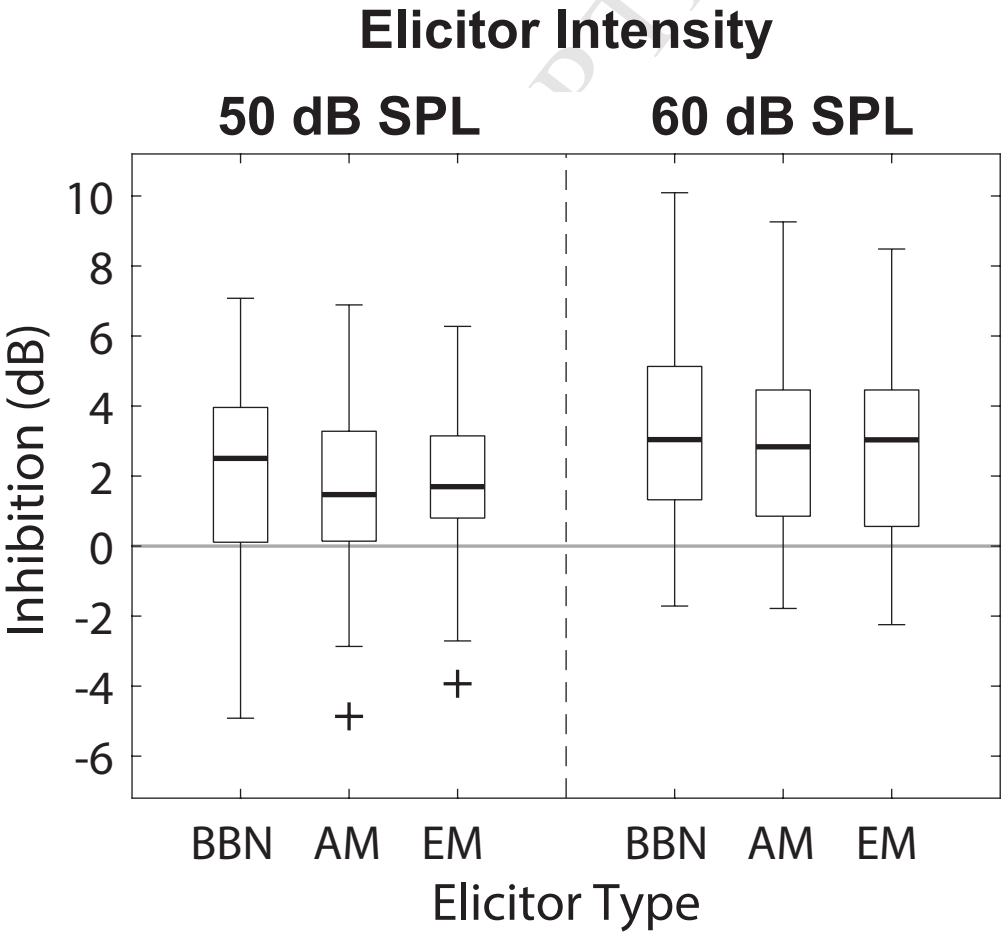

0.4
0.2
0
-0.2
-0.4
Amplitude (mPa)
8
10
12
14
16
18
Time (ms)
CAS-
CAS+

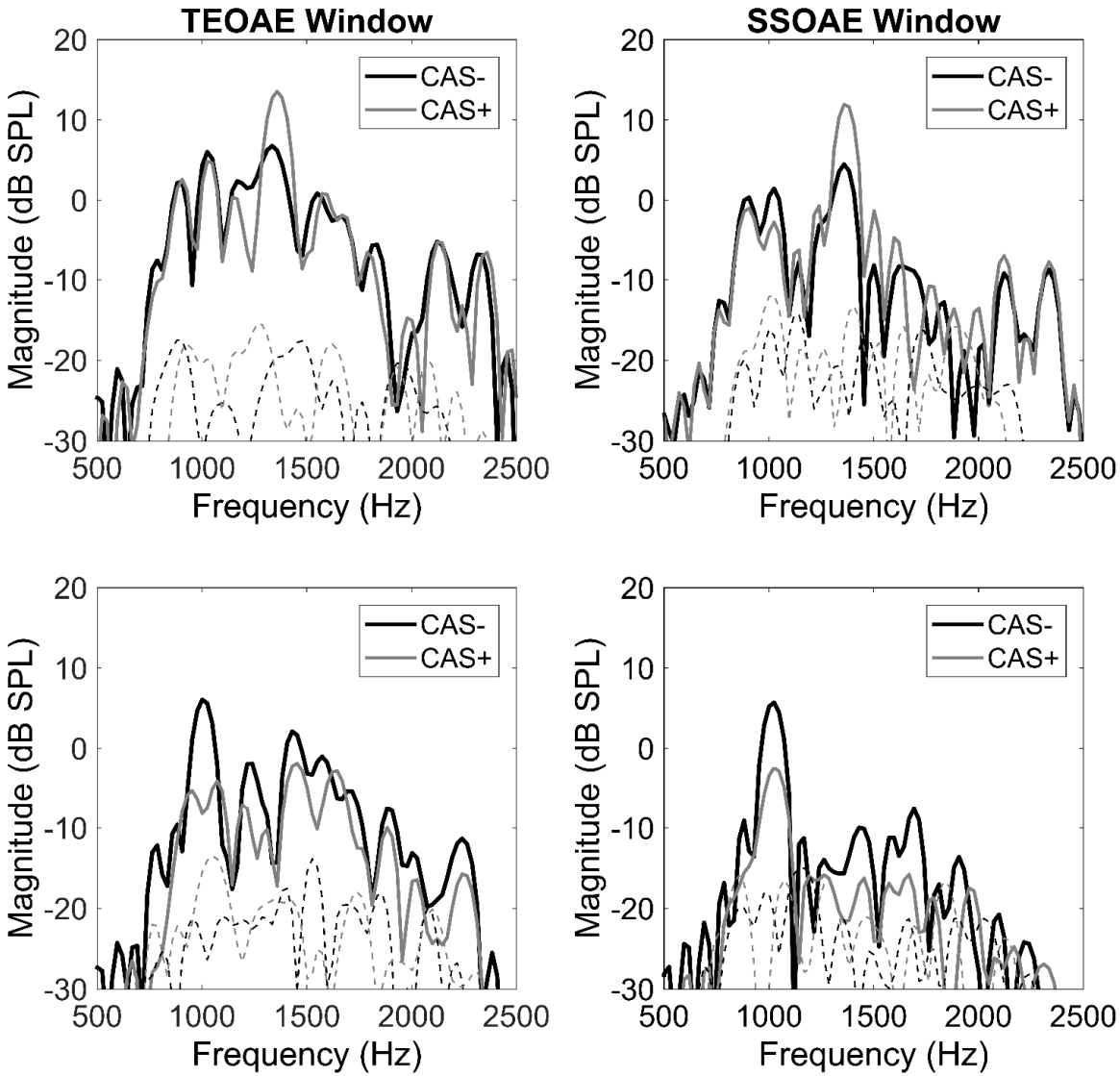


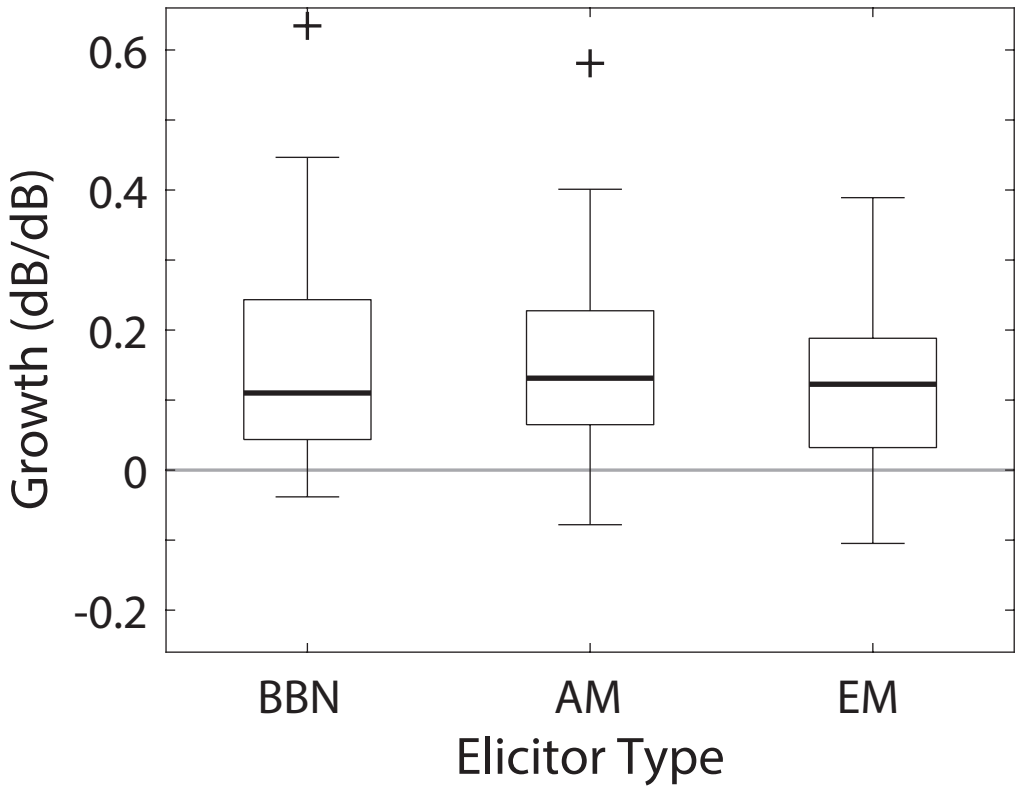

BBN
AM
EM
Inhibition (dB)
0
1
2
3
4
5
50
60
Elicitor Intensity (dB SPL)


Elicitor Intensity = 50 dB SPL
BBN
AM
EM
Inhibition (dB)
0
1
2
3
4
5
6
8-10
10-12
12-14
14-16
16-18
Analysis Window (ms)


Elicitor Intensity = 60 dB SPL
Inhibition (dB)
0
1
2
3
4
5
6
8-10
10-12
12-14
14-16
16-18
Analysis Window (ms)




TEOAE Window
SSOAE Window
CAS-
CAS+
Magnitude (dB SPL)
Frequency (Hz)
20
10
0
-10
-20
-30
500
1000
1500
2000
2500


0.6
0.4
0.2
0
-0.2
Growth (dB/dB)
BBN
AM
EM
Elicitor Type

Highlights

- MOCR responded similarly to dynamic and static noise elicitors
- MOCR enhanced rather than inhibited TEOAE amplitudes in minority of subjects
- Median MOCR growth was 0.11 – 0.13 dB per 1 dB increase in MOCR elicitor intensity