Concurrent measures of contralateral suppression of transient-evoked otoacoustic emissions and of auditory steady-state responses

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Concurrent measures of contralateral suppression of transient-evoked otoacoustic emissions and of auditory steady-state responses[a)]

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Contralateral suppression of otoacoustic emissions (OAEs) is frequently used to assess the medial olivocochlear (MOC) efferent system, and may have clinical utility. However, OAEs are weak or absent in hearing-impaired ears, so little is known about MOC function in the presence of hearing loss. A potential alternative measure is contralateral suppression of the auditory steady-state response (ASSR) because ASSRs are measurable in many hearing-impaired ears. This study compared contralateral suppression of both transient-evoked otoacoustic emissions (TEOAEs) and ASSRs in a group of ten primarily older adults with either normal hearing or mild sensorineural hearing loss. Responses were elicited using 75-dB peak sound pressure level clicks. The MOC was activated using contralateral broadband noise at 60 dB sound pressure level. Measurements were made concurrently to ensure a consistent attentional state between the two measures. The magnitude of contralateral suppression of ASSRs was significantly larger than contralateral suppression of TEOAEs. Both measures usually exhibited high test–retest reliability within a session. However, there was no significant correlation between the magnitude of contralateral suppression of TEOAEs and of ASSRs. Further work is needed to understand the role of the MOC in contralateral suppression of ASSRs. © *2016 Acoustical Society of America*. [http://dx.doi.org/10.1121/1.4962666]

[CA] Pages: 2027–2038

I. INTRODUCTION

Assessment of auditory efferent function holds promise for clinical applications, some of which include identifying the source of hearing-in-noise difficulties (Tokgoz-Yilmaz *et al.*, 2013), predicting susceptibility to noise-induced hearing loss (Maison and Liberman, 2000), and detecting the onset of presbycusis (Zhu *et al.*, 2007). Auditory efferent function is typically assessed using contralateral suppression of cochlear responses called otoacoustic emissions (OAEs) (Collet *et al.*, 1990). However, contralateral suppression measured in this way is often small in magnitude and may not be measurable in ears with hearing loss. As a result, little is known about the status of efferent function when there is damage to the peripheral auditory system. This study was developed to determine whether contralateral suppression of a measure of neural response, the auditory steady-state response (ASSR), might provide a more robust indication of auditory efferent activity than the more typically measured changes in OAEs.

The auditory efferent system modifies peripheral hearing function to improve sound detection in noise and to protect the periphery from acoustic trauma (for comprehensive reviews, see Guinan, 2006, 2011). The medial olivocochlear (MOC) branch of the auditory efferent system consists of fibers that predominately project from the medial superior olive to synapse on the outer hair cells (OHCs) of the opposite cochlea (Warr and Guinan, 1979). When the MOC system is stimulated by sound, MOC fibers release acetylcholine into the synaptic cleft, hyperpolarizing the OHCs. Because OHC motility forms the basis of the cochlear amplifier (Dallos, 1992), hyperpolarization of OHCs reduces the motility and thus the gain of the cochlear amplifier. In the case of transient sounds in the presence of background noise, the efferent-mediated reduction in cochlear amplifier gain reduces auditory nerve fiber responses to the continuous noise more than the responses to transient sounds, thus enhancing the detection of transient sounds in background noise (Winslow and Sachs, 1987; Guinan and Gifford, 1988; Kawase *et al.*, 1993).

In normal-hearing individuals, the amount of MOC activity is moderately correlated with the ability to understand speech in the presence of background noise (Giraud *et al.*, 1997; Kumar and Vanaja, 2004; de Boer and Thornton, 2008; Abdala *et al.*, 2014; Mishra and Lutman, 2014; Bidelman and Bhagat, 2015), lending further support to the hypothesis that the efferent system aids with hearing in noise. Clinical populations, such as hearing-impaired individuals, often experience significant difficulties

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communicating in background noise. It has been suggested that some hearing-in-noise problems could be due at least in part to compromised MOC function (Keppler *et al.*, 2010; Lisowska *et al.*, 2014). However, little is known about how the MOC system functions in ears with hearing loss, primarily due to methodologic barriers.

Nearly all previous studies have used OAEs to assess MOC function in humans. Presumably, OAEs are sounds generated as a by-product of cochlear amplification (Brownell, 1990), and can be noninvasively measured using a miniature probe microphone and loudspeaker placed in the external ear canal (Kemp, 1978). Activation of the MOC bundle reduces cochlear-amplifier gain, which is exhibited as decreased OAE levels (reviewed in Guinan, 2006). Contralateral suppression of OAEs is typically used to assess MOC activity, wherein OAEs are measured without and with contralateral acoustic stimulation (CAS) that activates the contralateral MOC pathway. Contralateral suppression has been described for all types of OAEs, including spontaneous otoacoustic emissions (SOAEs) (e.g., Mott *et al.*, 1989; Zhao and Dhar, 2010), stimulus frequency otoacoustic emissions (SFOAEs) (e.g., Guinan *et al.*, 2003; Lilaonitkul and Guinan, 2009; Zhao *et al.*, 2015), distortion-product otoacoustic emissions (DPOAEs) (e.g., Siegel and Kim, 1982; Moulin *et al.*, 1993; Abdala *et al.*, 2009; Deeter *et al.*, 2009), and transient-evoked otoacoustic emissions (TEOAEs) (e.g., Collet *et al.*, 1990; Hood *et al.*, 1996; Mertes and Goodman, 2016). Unlike DPOAEs, which are generated in the cochlea by two mechanisms, TEOAEs elicited by low to moderate stimulus levels are generated by only one cochlear mechanism (Shera and Guinan, 1999), which simplifies the interpretation of the TEOAE magnitude changes observed in the presence of CAS. Use of higher stimulus levels (which may be necessary for eliciting TEOAEs in hearing-impaired ears) can generate short-latency TEOAE components that may be due to nonlinear distortion (Moleti *et al.*, 2012) and/or basal reflections (Goodman *et al.*, 2011), but these components can be eliminated from analyses through time windowing procedures, which was the approach taken in the current study. Further, TEOAEs have the added advantage of being more easily measured in humans than SFOAEs, and TEOAEs are present in nearly all ears with normal hearing, unlike SOAEs (Kapadia and Lutman, 1997). Because of these notable advantages, TEOAEs were selected for examination in the current study.

Although contralateral suppression of OAEs is a convenient method for studying MOC function in normal-hearing ears, OAEs are often weak or absent in ears with hearing loss (Prieve *et al.*, 1993; Gorga *et al.*, 1997; Konrad-Martin *et al.*, 2002), which has limited studies of human MOC function to individuals with normal or near-normal hearing. The result is that little is known about the MOC system in ears with hearing loss. Alternative assessments of MOC function in hearing-impaired ears are therefore warranted. One potentially feasible measure of MOC activity is contralateral suppression of the auditory steady state response (ASSR). The ASSR is a measure of neural phase locking in response to modulations in the amplitude and/or frequency of a stimulus (Galambos *et al.*, 1981). The ASSR is typically measured using scalp electrodes and is exhibited as a peak in the electroencephalography (EEG) spectrum that corresponds precisely to that of the stimulus modulation frequency. The ASSR is generated by subcortical structures and can also include contributions from cortical structures at stimulus modulation rates less than approximately 60 Hz (Kuwada *et al.*, 2002).

There are several reasons why contralateral suppression of ASSRs may be a promising tool for studying MOC activity. First, ASSRs can be measured at suprathreshold stimulus levels in ears with significant hearing loss and demonstrate similar amplitudes as normal-hearing individuals (Rodriguez *et al.*, 1986; Vander Werff and Brown, 2005; Leigh-Paffenroth and Murnane, 2011). Second, ASSR amplitudes decrease in the presence of contralateral noise (Maki *et al.*, 2009; Kawase *et al.*, 2012; Kiyokawa *et al.*, 2012; Usubuchi *et al.*, 2014), which may be due at least in part to MOC activity. Third, contralateral suppression of auditory neural responses is often larger than contralateral suppression of OAEs (Puria *et al.*, 1996; Chabert *et al.*, 2002; Lichtenhan *et al.*, 2016). Larger contralateral suppression values may be more easily detected in hearing-impaired ears than smaller changes and could therefore be more useful clinically, relative to the smaller contralateral suppression values observed with OAE measures.

The extent to which contralateral suppression of the ASSR involves the MOC system is not known at this time. A previous study found that 40-Hz, but not 80-Hz, ASSR detection thresholds were significantly elevated in the presence of CAS (Maki *et al.*, 2009). The authors argued that if the MOC were involved, it would have affected both the 40- and 80-Hz ASSRs because they are both generated by subcortical structures that should be inhibited by MOC activation. Alternatively, it is possible that an effect was only seen for 40-Hz ASSRs because the response amplitudes and signal-to-noise ratios (SNRs) are larger than at 80-Hz (Purcell and Dajani, 2008), which are important considerations for being able to detect small MOC-induced changes in response amplitude (Goodman *et al.*, 2013). Additionally, Maki *et al.* (2009) did not assess MOC activity via OAEs, so the extent of MOC activation in their subjects cannot be ascertained.

As an initial step toward examining the role of the MOC in contralateral suppression of ASSRs, the current study compared contralateral suppression of ASSRs with contralateral suppression of TEOAEs in response to suprathreshold stimuli in a group of adults with normal hearing or with mild hearing loss. Because ASSRs can be generated in response to a click train, where the ASSR occurs at the frequency corresponding to the click rate (Galambos and Makeig, 1992), ASSRs and TEOAEs were elicited with the same click stimuli. Additionally, ASSRs and TEOAEs were measured concurrently using an interleaving paradigm to ensure that subject attention and alertness were identical across the two measurements and to allow for verification that the MOC was activated in individual subjects (via contralateral suppression of TEOAEs). Because MOC activity can be modulated by changes in arousal and attention (Froehlich *et al.*,

1993; Maison *et al.*, 2001; de Boer and Thornton, 2007; Smith and Cone, 2015), it was important to ensure that there were no differences in subject state between the two types of measurements by using a concurrent data-collection protocol.

It was hypothesized that both response measures would demonstrate high test–retest reliability within a session, based on previous studies of MOC test–retest reliability (Mishra and Lutman, 2013; Mertes and Goodman, 2016). It was further postulated that contralateral suppression of ASSRs would be significantly larger than contralateral suppression of TEOAEs, as was demonstrated for contralateral suppression of auditory nerve responses (Puria *et al.*, 1996; Chabert *et al.*, 2002; Lichtenhan *et al.*, 2016). Finally, it was hypothesized that the MOC-based modifications in both measures would be significantly correlated. A larger reduction in OHC motility (i.e., larger contralateral suppression of TEOAEs) should diminish the stimulation to progressively higher auditory centers, thus resulting in greater contralateral suppression of the ASSR.

II. METHODS

A. Subjects

Ten adult subjects (nine males) were recruited from the VA Loma Linda Healthcare System and the surrounding community. Subject ages ranged from 34 to 70 yrs [mean = 54.3 yrs, standard deviation (SD) = 12.9]. All subjects had an unremarkable otoscopic examination, immittance audiometry results within normal clinical limits, three-frequency (500, 1000, and 2000 Hz) pure-tone averages ≤25 dB hearing level (HL), no air-bone gaps >10 dB at two or more frequencies, and no history of conductive hearing disorders. Mean audiometric thresholds and standard errors of the mean (SEMs) for the left and right ears are shown in Fig. 1. Before beginning the experiment, all subjects demonstrated measurable TEOAEs and ASSRs with an SNR of >6 dB. The study protocol was approved by the VA Loma Linda Healthcare System's Institutional Review Board and written informed consent was obtained from all subjects prior to their enrollment in the study. All subjects received monetary compensation for their participation.

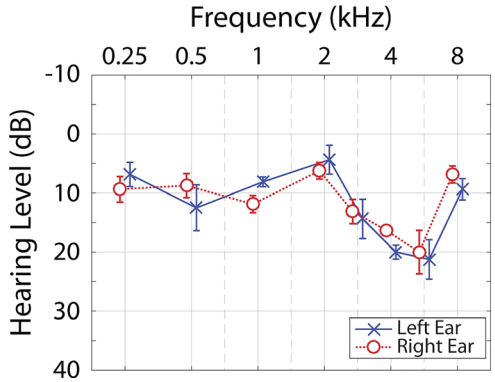

FIG. 1. (Color online) Mean audiometric thresholds for the left and right ears. Error bars represent ±1 SEM. Results for the left and right ears are offset from each other at a given frequency to aid visualization.

B. Equipment

All testing was conducted in a double-walled sound-attenuating booth (Industrial Acoustics Company, Bronx, NY) with subjects seated comfortably in a recliner. Pure-tone air-conduction thresholds were measured at octave frequencies from 0.25 to 8 kHz as well as interoctave frequencies of 3 and 6 kHz using an Astera^2 audiometer (GN Otometrics, Taastrup, Denmark). Immittance measures were performed using a GSI TympStar immittance bridge (Grason-Stadler, Eden Prairie, MN).

For TEOAE and ASSR testing, stimulus presentation and response acquisition were achieved using an RZ6 I/O processor [Tucker-Davis Technologies (TDT), Alachua, FL] interfacing with a WS4 workstation (TDT) controlled by custom code written in the MATLAB (MathWorks, Natick, MA) and RPvdsEx (TDT) programming languages. Digitally-generated stimuli were routed from the processor to two PA5 programmable attenuators (TDT) and then to a pair of ER-2 insert earphones (Etymōtic Research, Elk Grove Village, IL). The left earphone was inserted in the left ear and the sound tubing of the right earphone was connected to an ER-10B+ OAE probe microphone assembly (Etymōtic Research) that was inserted in the right ear. The ER-10B+ microphone amplifier was set to +40 dB gain. The microphone signal was sampled at a rate of 24414.0625 Hz (the default sampling rate of the RZ6 processor). ASSR recordings were implemented using scalp electrodes connected to an RA4LI headstage (TDT) and an RA4PA preamplifier (TDT). Single-channel ASSR recordings were made with an active electrode placed on the high forehead (Fz), a reference electrode placed on the right mastoid (M2), and a ground electrode placed on the low forehead (Fpz). The EEG signal was sampled at a rate of 939 Hz.

C. Experimental stimuli

TEOAEs and ASSRs were measured concurrently using the RZ6 processor and RPvdsEx software. A cartoon of the measurement setup is shown in Fig. 2. TEOAEs and ASSRs were elicited by 80-μs clicks presented at 75 dB peak sound pressure level (pSPL) at a rate of 39.0625/s (selected to yield an integer number of samples based on the sampling rate, but nominally referred to hereafter as 40 Hz). Click stimuli were generated by the RZ6 I/O processor.

MOC activation was achieved using broadband Gaussian noise generated by the RZ6 I/O processor at the sampling rate noted above. The noise was presented to the ear opposite to the click-stimulated ear, and the noise will be referred to as CAS to be consistent with previous literature. The CAS was presented at an overall root-mean-square (RMS) level of 60 dB(A) sound pressure level (SPL). This level was selected based on previous work demonstrating that it is an effective activator of the MOC (e.g., Guinan *et al.*, 2003; Mertes and Goodman, 2016) while minimizing elicitation of the middle-ear muscle reflex (MEMR), which can confound the interpretation of changes in both OAE levels and stimulus levels (Goodman *et al.*, 2013) as discussed below. The SPL of the CAS was calibrated in an AEC202 2-cc coupler (Larson Davis, Depew, NY).

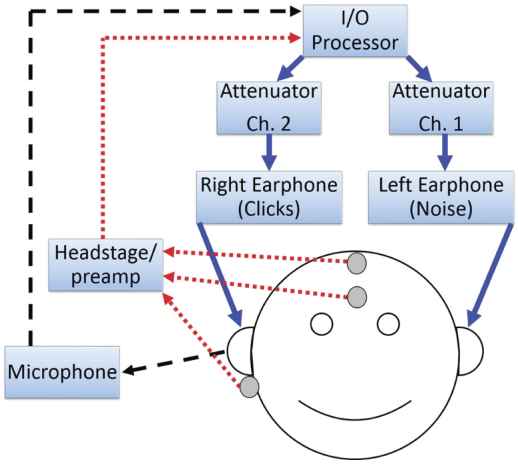

FIG. 2. (Color online) Schematic of the equipment setup for concurrent measurement of contralateral suppression of ASSRs and of TEOAEs. Stimulus outputs are represented by solid arrows. Input from the ER-10B+ microphone is represented by a dashed black arrow. Inputs from the electrode headstage and preamplifier are represented by the dotted arrows.

D. TEOAE and ASSR recording procedure

Prior to each recording, all electrode impedances were verified to be $\leq 5\,\text{k}\Omega$, with no more than a 2-kΩ difference among electrode impedances. Additionally, the click-stimulus levels were calibrated in subjects' ear canals to be within ± 0.3 dB of the target level of 75 dB pSPL before each recording began. In each subject, the clicks were presented to the right ear while the CAS was presented to the left ear, because larger MOC-induced changes in OAE magnitudes have been demonstrated in this configuration, relative to presenting clicks in the left ear and CAS in the right ear (Khalfa *et al.*, 1997). To remove low-frequency acoustic noise during the recording prior to saving the data to disk, the ER-10B+ microphone signal was high-pass filtered with a second-order Butterworth filter with a cutoff frequency of 250 Hz.

Each recorded set of TEOAEs and ASSRs consisted of waveforms obtained in two conditions: without CAS and with CAS (referred to hereafter as *no CAS* and *CAS*, respectively). Because the index of MOC function was the magnitude differences between the two conditions, it was crucial to minimize potential differences between waveform amplitudes in the two conditions not due to CAS (e.g., drift in stimulus levels, TEOAE levels, and/or ASSR levels across time; Goodman *et al.*, 2013). Therefore, the two conditions were interleaved across the recording duration so that any drifts would be distributed across measurements made in both conditions.

A schematic of an interleaved stimulus recording is shown in Fig. 3. The *no CAS* condition (i.e., only clicks presented in the right ear) came first, followed by 2 s of the contralateral noise to allow for the full onset of the MOC reflex (Backus and Guinan, 2006). The *CAS* condition (i.e., clicks presented in the right ear and broadband noise presented in the left ear) was then presented, followed by 2 s of silence to permit a full offset of the MOC reflex (Backus and Guinan, 2006) before the sequence was repeated.

The stimulus presentation represented in Fig. 3 was repeated 10 times, for a total test time of 11.3 min for one recording set. The click-stimulus levels, as measured in the ear canal using the ER-10B+ microphone, were monitored visually by the experimenter in real-time to ensure stimulus stability. After the first recording set was completed, the earphones were removed and the subject was provided with a 5-min break, followed by a second recording set in order to compute within-session test–retest reliability. The experimenter attempted to place the ER-10B+ probe in a similar location in the ear canal for both measurements.

To ensure that subjects had a consistent attentional state during the recordings, subjects participated in a visual-attention task described by Mertes and Goodman (2016). Specifically, subjects watched a computer screen inside the sound booth and were instructed to quietly click a mouse button as soon as possible when the computer screen turned blue, which happened every 1–4 s, selected from a random uniform distribution. The ER-10B+ microphone cable was situated away from subjects' bodies to reduce measured vibrations that may have occurred due to subjects' use of the mouse during recordings. Subjects were provided with visual feedback regarding their reaction times during the task so they could monitor their performance. The experimenter also monitored subject performance so that any changes in performance across time were identified (which may have been due to drifts in attention), and which alerted the experimenter to provide the subject with a short break. In addition to allowing for monitoring of a subject attentional state, the

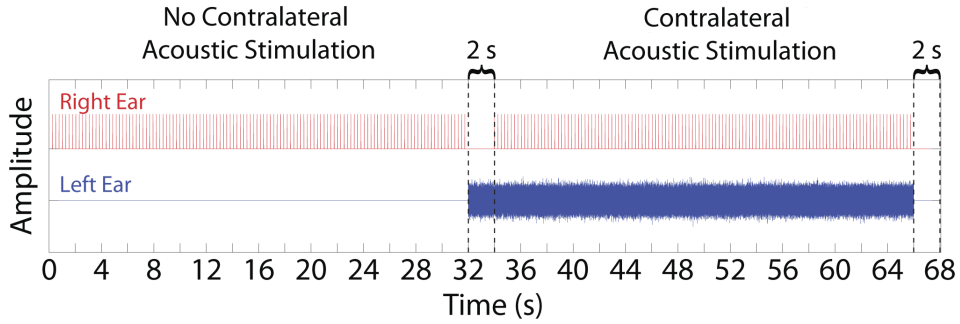

FIG. 3. (Color online) Schematic of one interleaved presentation of stimuli. Click trains are shown in the top half of the panel for the right ear and broadband contralateral noise is shown in the bottom half of the panel for the left ear. The number of clicks displayed is reduced by a factor of 10 to aid visualization of individual click stimuli. Two stimulus conditions (*no CAS* and *CAS*) are shown, separated by a 2-s noise-alone interval (first pair of vertical dashed lines). The two stimulus conditions were repeated continuously, with 2 s of silence between repetitions (second pair of vertical dashed lines). Note that TEOAEs and ASSRs were measured concurrently for the duration of the recording.

visual task was implemented because work in both humans and animals suggest that MOC activity is increased during a visual task (Puel *et al.*, 1988; de Boer and Thornton, 2007; Delano *et al.*, 2007), which should increase the detectability of an MOC-induced change in TEOAE levels relative to no task. The visual task was implemented throughout the entire recording so that subjects were actively engaged during both the *no CAS* and *CAS* conditions; therefore, differences in attention between the two conditions were minimized.

E. Middle-ear muscle reflex check

Prior to processing and analyzing the ASSR and TEOAE waveforms, it was important to determine if there was evidence of the activation of the MEMR caused by the introduction of CAS. If the MEMR is activated when the CAS is turned on, the impedance characteristics of the middle-ear system are altered, which can in turn modify OAE levels and measured stimulus levels (Whitehead *et al.*, 1991). If the MEMR is stimulated in an OAE-based test of MOC function, it is difficult to ascertain whether the change in OAE level was due to activation of the MOC, of the MEMR, or a combination (Guinan *et al.*, 2003; Goodman *et al.*, 2013). Studies have detected activation of the MEMR by comparing the stimulus level measured in the ear canal in the *CAS* versus *no CAS* conditions (Guinan *et al.*, 2003; Zhao and Dhar, 2010; Abdala *et al.*, 2013; Goodman *et al.*, 2013; Boothalingam and Purcell, 2015; Lichtenhan *et al.*, 2016; Mertes and Goodman, 2016). Changes in stimulus level exceeding a criterion amount were attributed to alterations in middle-ear impedance caused by MEMR activation induced by the CAS. In the current study, MEMR activation was identified if the absolute value of the mean difference in stimulus levels between the *no CAS* and *CAS* exceeded 0.14% (Abdala *et al.*, 2013). However, no subjects were identified as having MEMR activation and therefore the results of the MEMR check will not be discussed further. It must be noted that this MEMR check cannot be used to detect if the click stimuli themselves were eliciting the MEMR, so it is possible that there was MEMR activation in both the *no CAS* and *CAS* conditions due to the clicks, but not due to the introduction of CAS.

F. Data pre-processing

After the MEMR check was completed, the recorded ASSR and TEOAE waveforms were each sorted to form two matrices of waveforms in the *no CAS* and *CAS* conditions, each 320 s in duration (recall that there were 10 interleaves consisting of 32 s in each condition). The time vector associated with the individual waveform buffers was set so that time zero was in reference to the time corresponding to the maximum amplitude of the click stimulus. Both ASSR matrices were reshaped into 320 buffers that were 1 s in duration, and both TEOAE matrices were reshaped into 12 500 buffers that were 20 ms in duration. The first 3.5 ms of the TEOAE waveforms were zeroed out to remove stimulus artifact. To reduce frequency splatter in the frequency domain analysis, all waveforms were ramped on and off with raised-cosine ramps (ASSRs: duration = 50 ms; TEOAEs: duration = 2.5 ms). For the TEOAE waveforms, the onset ramps were applied beginning at 3.5 ms post-stimulus onset. Waveforms were bandpass filtered digitally using a Hann window-based filter design (ASSRs: passband = 30–50 Hz, filter order = 1024; TEOAEs: passband = 1000–4000 Hz, filter order = 256). Artifact rejection was performed *post hoc* to remove individual buffers with excessively high or low amplitudes. Any ASSR buffer in which the peak amplitude exceeded $\pm 10\,\mu$V was rejected. Any ASSR or TEOAE buffer in which the peak and RMS amplitudes fell outside 1.5× the interquartile range were also rejected (Goodman *et al.*, 2009). Following artifact rejection, each ASSR matrix was reshaped into 20 buffers that were each 16 s in duration, allowing for increased frequency resolution relative to 1-s buffers. To obtain estimates of the signal and the noise floor, the matrices of the ASSR and TEOAE waveforms in both the *no CAS* and *CAS* conditions were divided into two equally-sized buffers, A and B (odd- and even-numbered waveforms, respectively). The estimate of the signal was obtained as $(A+B)/2$, and the noise floor estimate was computed as $(A-B)/2$ (Kemp *et al.*, 1990).

G. Quantification of contralateral suppression

Contralateral suppression of ASSRs and of TEOAEs was analyzed in the frequency domain. An example of TEOAE and ASSR spectra obtained in the *no CAS* and *CAS* conditions is shown in Fig. 4. The two replicates of each measurement for each subject were averaged, and fast Fourier transforms (FFTs) were computed on the mean signal and noise floor waveforms for ASSRs and TEOAEs in the *no CAS* and *CAS* conditions. The bin widths of the FFTs were 0.0625 Hz for ASSRs and 11.92 Hz for TEOAEs. To compare the size of contralateral suppression of ASSRs to

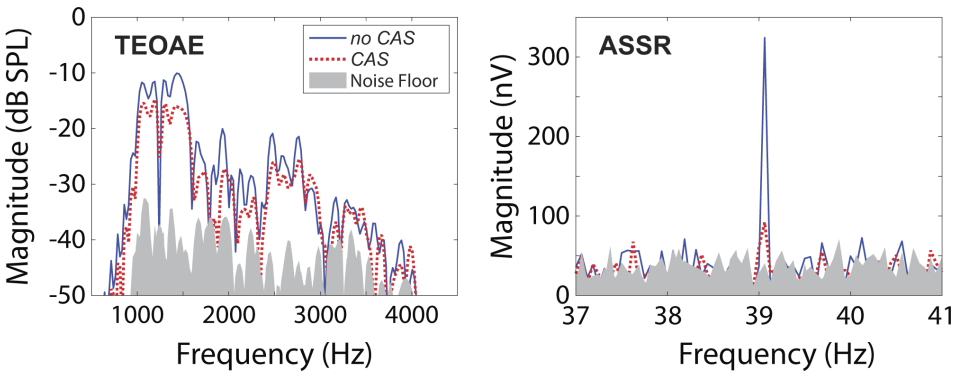

FIG. 4. (Color online) Recorded TEOAE and ASSR spectra (left and right panels, respectively) for one representative subject. Solid lines represent responses obtained in the *no CAS* condition. Dotted lines represent responses obtained in the *CAS* condition. The filled gray regions represent the recording noise floors.

that of TEOAEs, contralateral suppression of each measure was expressed as a single value in the same unit of measurement. TEOAE levels are typically expressed in dB SPL, whereas ASSR amplitudes are routinely expressed in nV. The relative change in magnitude between the *no CAS* and *CAS* conditions was expressed in decibels for both measures. TEOAEs are observed across a broad frequency range, but the ASSR occurs at a single frequency (39.0625 Hz); therefore, the magnitude change in TEOAEs was reduced to a single value by converting magnitude to linear units (mPa) and summing the magnitude from 1000–4000 Hz. The magnitude at a given TEOAE frequency was included in the summing operation only if the SNR at that frequency was >6 dB in both the *no CAS* and *CAS* conditions. The summed TEOAE amplitudes for the *no CAS* and *CAS* conditions were converted to decibels, and contralateral suppression was computed by subtracting the summed magnitudes in dB (*no CAS-CAS*). For ASSRs, the magnitude values were converted from nV to dB, and contralateral suppression was computed by subtracting the magnitudes in dB (*no CAS-CAS*). In the example shown in Fig. 4, contralateral suppression of TEOAEs was 3.75 dB and contralateral suppression of ASSRs was 10.92 dB. A larger value of contralateral suppression indicated a greater reduction in response magnitude in the presence of CAS.

III. RESULTS

A. TEOAE and ASSR magnitudes

Figure 5 shows TEOAE and ASSR response magnitudes in the *no CAS* and *CAS* conditions for all individual subjects. For each subject, the mean signal and noise floor magnitudes were computed across the two measurements. For this figure, the magnitudes are expressed in the typical units for each measurement (dB SPL for TEOAEs, nV for ASSRs). Tables I and II show descriptive statistics (means, SDs, minima, and maxima) for TEOAE and ASSR group data, respectively. In both the *no CAS* and *CAS* conditions, all subjects had measurable TEOAEs and ASSRs, as evidenced by SNRs >6 dB. Additionally, these SNRs were sufficiently high for detecting small magnitude changes due to CAS (Goodman *et al.*, 2013).

B. Test–retest reliability of contralateral suppression

To more directly compare the size of contralateral suppression of TEOAEs to that of ASSRs, contralateral suppression of both measures was expressed in dB. Within-session test–retest reliability of contralateral suppression was analyzed for both measures by computing the correlation between contralateral suppression at the first and second measurements. Results shown in Fig. 6 revealed high test–retest reliability as evidenced by a strong correlation for contralateral suppression of TEOAEs, $r = 0.98$, $p < 0.01$, and of ASSRs, $r = 0.84$, $p < 0.01$. These results were consistent with the hypothesis that test–retest reliability would be high for both measures.

It must be noted that Subject 6 showed poor test–retest reliability for contralateral suppression of the ASSR. The magnitude increased by 1.24 dB at the first measurement (opposite of the expected direction) and decreased by 1.22 dB at the second measurement (the expected direction). No other subjects demonstrated this inconsistency in contralateral suppression of ASSRs. Additional repeated measures in this subject (not shown) continued to exhibit inconsistent magnitude increases and decreases of the ASSR. The reason for this variability in results was unclear because this subject demonstrated sufficient ASSR magnitudes and SNRs (see right panel of Fig. 5), and also showed consistent CAS-induced suppression of TEOAEs. Despite these inconsistencies, this subject's results were included so that the group data were representative of all subjects tested.

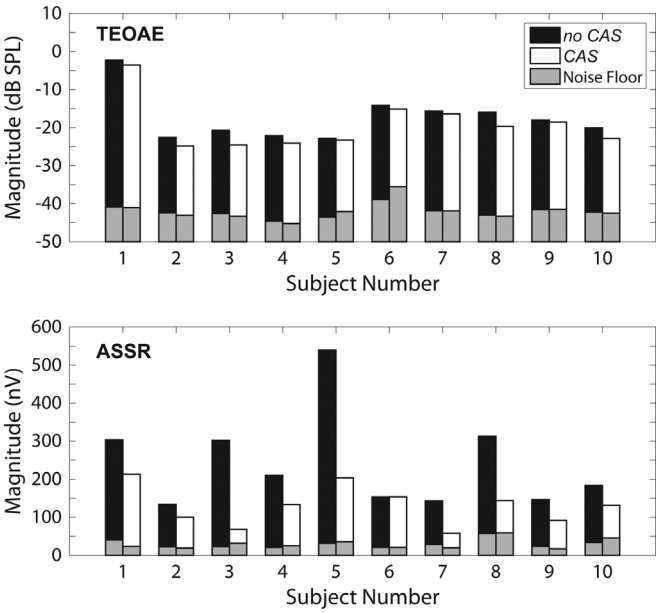

FIG. 5. Magnitudes of TEOAEs and ASSRs (top and bottom panels, respectively) for each individual subject. Responses in the *no CAS* and *CAS* conditions are represented by black and white bars, respectively. The recording noise floors are represented by gray bars; noise floors in the *no CAS* and *CAS* conditions are on the left and right side, respectively, for each individual subject. The magnitudes displayed here represent the mean computed across the two replicate measurements obtained from each subject.

C. Relative magnitude of contralateral suppression

Because there was high test–retest reliability in contralateral suppression of TEOAEs and of ASSRs, the mean contralateral suppression value for the two repeated measurements was computed for each subject and experimental task, and this mean value will be reported hereafter. Comparisons of contralateral suppression of TEOAEs and of

TABLE I. Descriptive statistics for TEOAE group data for the parameters of signal magnitude, noise-floor magnitude, and SNR. Results are displayed to facilitate comparison between the *no CAS* and *CAS* conditions for each parameter. Means, minima, and maxima are in dB SPL. SNRs and SDs are in dB.

Parameter	Condition	Mean	SD	Minimum	Maximum
Signal	*no CAS*	−17.4	6.2	−22.8	−2.3
	CAS	−19.3	6.5	−24.8	−3.6
Noise Floor	*no CAS*	−42.2	1.5	−44.6	−38.9
	CAS	−41.9	2.5	−45.2	−35.6
SNR	*no CAS*	24.7	5.4	19.8	38.6
	CAS	22.7	5.7	18.2	37.4

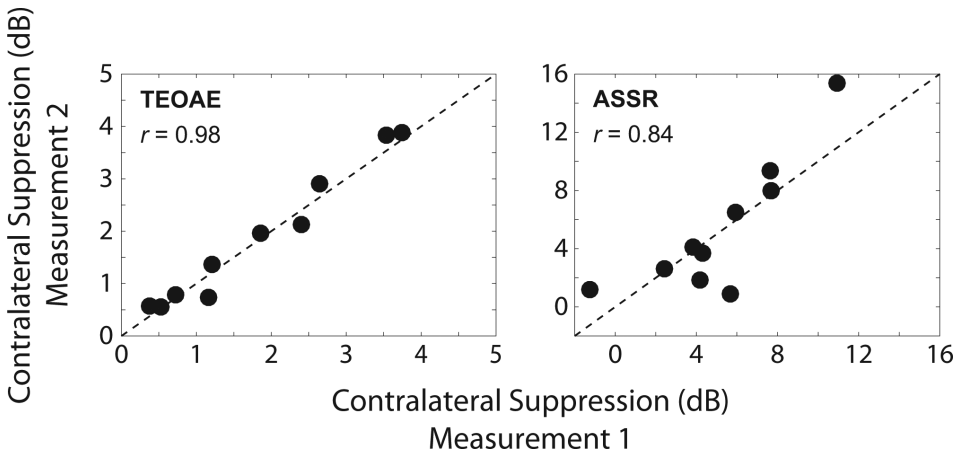

FIG. 6. Test–retest reliability of contralateral suppression of TEOAEs (left panel) and of ASSRs (right panel). Results are plotted as the contralateral suppression value obtained in the second measurement against that of the first measurement (note the different ordinate scales). The filled circles represent data from each individual subject. The dashed line represents a 1:1 correspondence between the results at each measurement. Both measures exhibited high test–retest reliability within a session.

ASSRs are shown in Fig. 7 for each individual subject and for the group data. As expected, all subjects showed a decrease in the magnitudes of TEOAEs and of ASSRs in the presence of CAS (with the exception of Subject 6, as described above). Contralateral suppression of TEOAEs ranged from 0.5 to 3.8 dB [mean = 1.8 dB, SD = 1.3], while contralateral suppression of ASSRs ranged from −0.01 to 13.1 dB [mean = 5.2 dB, SD = 3.8]. It can be seen from Fig. 7 that there was considerable intersubject variability regarding the size of the difference between contralateral suppression of TEOAEs and of ASSRs. However, a paired-samples t-test indicated that contralateral suppression of ASSRs was significantly larger in magnitude than contralateral suppression of TEOAEs, $t(9) = -3.0441$, $p < 0.05$, consistent with the hypothesized result.

D. Association between contralateral suppression of TEOAEs and of ASSRs

Although contralateral suppression of ASSRs was larger than of TEOAEs, it was of interest to examine the association between the two measures. A strong correlation would suggest that both measures assess MOC activity. Furthermore, it might suggest that contralateral suppression of ASSRs could be used in place of contralateral suppression of TEOAEs, which would be useful in ears with sensorineural hearing loss, which demonstrate absent TEOAEs (e.g., Prieve *et al.*, 1993), but measurable ASSRs (e.g., Vander Werff and Brown, 2005). The association between contralateral suppression of TEOAEs and of ASSRs is shown in Fig. 8. There was a trend of increasing contralateral suppression of ASSRs with increasing contralateral suppression of TEOAEs, but there was no significant correlation between the two measures, $r = 0.34$, $p = 0.33$, contrary to the hypothesized result.

TABLE II. Descriptive statistics for ASSR group data for the parameters of signal magnitude, noise-floor magnitude, and SNR. Table format is identical to that of Table I, except that all values are in nV.

Parameter	Condition	Mean	SD	Minimum	Maximum
Signal	*no CAS*	242.9	126.4	133.8	539.3
	CAS	129.7	52.2	58.0	213.4
Noise floor	*no CAS*	30.1	11.6	20.6	57.4
	CAS	29.7	13.7	16.9	59.1
SNR	*no CAS*	212.8	122.3	111.8	507.7
	CAS	100.0	50.8	36.1	190.2

IV. DISCUSSION

A. Feasibility of concurrent measurements

The purpose of this study was to determine if contralateral suppression of the ASSR can be used as a metric of MOC activity. Concurrent measurements were made to reduce the effects of subject attention, which can impact the strength of MOC activity (Maison *et al.*, 2001; de Boer and Thornton, 2007). This study demonstrated that concurrent measurements are feasible in a relatively short duration of 11 min. Several studies have described methods for concurrently measuring DPOAEs and ASSRs (Purcell *et al.*, 2003; Oswald *et al.*, 2006; Rosner *et al.*, 2011; Wittekindt *et al.*, 2014). However, to the authors' knowledge, the present study is the first to report concurrent measurements of TEOAEs and of ASSRs for the purpose of examining contralateral suppression.

B. Contralateral suppression of cochlear versus neural responses

Contralateral suppression of TEOAEs was measurable in all subjects, as expected. The range of values for contralateral suppression of TEOAEs was consistent with previous reports (e.g., Collet *et al.*, 1990; Hood *et al.*, 1996; de Ceulaer *et al.*, 2001; Goodman *et al.*, 2013). Test–retest reliability was also high, as expected based on previous work

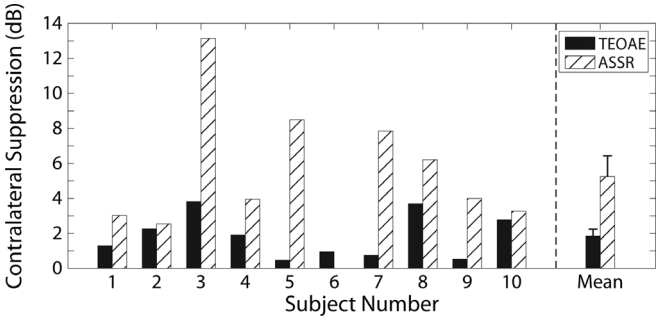

FIG. 7. Contralateral suppression of TEOAEs (black bars) and of ASSRs (hatched bars). Individual subject data are plotted to the left of the vertical dashed line. The mean data (+1 SEM) are plotted to the right of the dashed line. Note that Subject 6 showed close to 0 dB (−0.01 dB) of contralateral suppression of the ASSR and thus no hatched bar is apparent for this subject.

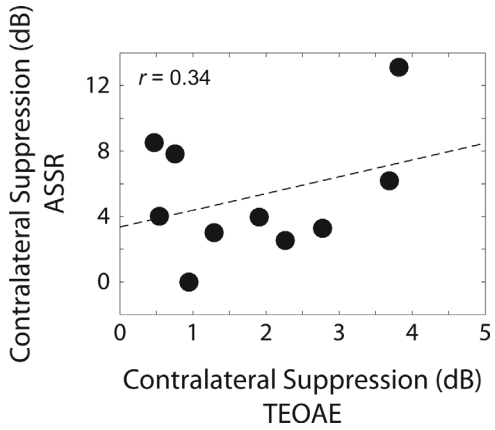

FIG. 8. Association between contralateral suppression of TEOAEs and of ASSRs. The filled circles represent data from individual subjects. The dashed line represents a least-squares fit to the data. The correlation between the two measures was not significant.

(Mishra and Lutman, 2013; Mertes and Goodman, 2016), although further work is needed to establish test–retest reliability across longer time periods. Contralateral suppression of ASSRs was measured reliably in nine of ten subjects.

It was unclear why Subject 6 demonstrated large inconsistencies in how the ASSR changed in the presence of CAS (i.e., both magnitude decreases and increases were exhibited across repeated measures). Previous studies have reported that a minority of subjects can exhibit TEOAE magnitude increases, rather than decreases, in the presence of CAS (e.g., Hood *et al.*, 1996; Goodman *et al.*, 2013). Additionally, subcortically-generated envelope following responses can demonstrate magnitude enhancements in the presence of contralateral noise (Bharadwaj *et al.*, 2015). Suppression of OAE levels in the presence of enhancements in ASSR levels could be reflective of more complicated processes contributing to the ASSR, relative to the TEOAEs. However, these magnitude increases would be expected to be consistent across repeated measures (Mertes and Goodman, 2016), but Subject 6 demonstrated inconsistent magnitude increases and decreases across six repeated measures (not shown). These variable results could not be attributed to poor hearing thresholds (all thresholds were $\leq$25 dB HL), lack of contralateral suppression of TEOAEs, poor ASSR SNRs, equipment problems, or variable attentional states during measurements. It is possible, but unlikely, that some factor not accounted for by the inclusion/exclusion criteria, perhaps related to medical history, could have contributed to the variable results.

When associating MOC activity with auditory perception, the most relevant effect is on the neural output (Guinan, 2014). The finding of larger contralateral suppression of ASSRs than of TEOAEs appears consistent with previous reports showing that the MOC can exhibit larger effects on neural responses than on OAEs (Puria *et al.*, 1996; Chabert *et al.*, 2002; Lichtenhan *et al.*, 2016). These previous studies examined the effect of MOC stimulation on the compound action potential (CAP) in humans or in animals. Larger changes in the neural responses suggest that OAE-based measures of the MOC may underestimate the magnitude of the MOC effect on the neural response.

While it may therefore appear to be advantageous to use the CAP to assess MOC activity, these measurements have been acknowledged to require long data-collection times (10 h) to detect an MOC-induced amplitude change (Lichtenhan *et al.*, 2016). The concurrent measurements of TEOAEs and of ASSRs made in the current study have the advantage of being obtained in a matter of minutes rather than hours. Faster data collection times are also advantageous to reduce attentional drifts and changes in probe position over time (Goodman *et al.*, 2013).

C. The role of the MOC in contralateral suppression of the ASSR

Contralateral suppression of the 40-Hz ASSR has been demonstrated previously (Galambos and Makeig, 1992; Maki *et al.*, 2009; Kawase *et al.*, 2012; Kiyokawa *et al.*, 2012; Usubuchi *et al.*, 2014). However, the physiologic source of the contralateral-suppression effect has yet to be determined. Several studies have argued that the suppression is a result of neural centers above the level of the brainstem because CAS did not inhibit the wave V amplitude of the auditory brainstem response (Galambos and Makeig, 1992), nor did it alter detection thresholds of the 80-Hz ASSR (Maki *et al.*, 2009), which are both generated by subcortical structures (Møller, 1998; Kuwada *et al.*, 2002). However, other studies have shown that CAS alters the amplitude and latency of wave V in humans (Sininger and Cone-Wesson, 2006; Schochat *et al.*, 2012). Furthermore, animal studies have shown that MOC stimulation can alter activity of the cochlear nucleus, superior olivary complex, and inferior colliculus (Desmedt, 1962; Starr and Wernick, 1968; Mulders *et al.*, 2008; Seluakumaran *et al.*, 2008), demonstrating that the MOC can affect brainstem function.

In the current study, the correlation between contralateral suppression of TEOAEs and of ASSRs was weak and non-significant, suggesting that contralateral suppression of the ASSR may not serve as a substitute measure for contralateral suppression of TEOAEs to assess MOC activity in hearing-impaired ears. It is possible that the non-significant finding was due to low statistical power. It is also possible that contralateral suppression of TEOAEs and of ASSRs tap into different aspects of MOC activity. As discussed above, contralateral suppression of OAEs may underestimate the effect of MOC activity on neural responses, but previous studies (Puria *et al.*, 1996; Lichtenhan *et al.*, 2016) did not report the correlation between the magnitude of contralateral suppression of DPOAEs and CAPs.

Another potential complication involves MOC collaterals to the cochlear nucleus. Because these collaterals lie beyond the OHCs, it is possible that MOC effects on neural function would be exhibited differently from MOC effects on cochlear function and thus not be correlated. MOC collaterals have been demonstrated in non-human animals such as cats and guinea pigs (Brown *et al.*, 1988; Mulders *et al.*, 2009). However, such collaterals have not been observed in humans (Moore and Osen, 1979), so this does not appear to explain

the discrepant results between contralateral suppression of ASSRs and of TEOAEs. Complex level-dependent effects of MOC activation on inner hair cell activity have been described recently (Guinan, 2012), so the hypothesis that contralateral suppression of TEOAEs and of ASSRs are linearly correlated may have been too simplistic to characterize the relationship between MOC effects on the peripheral and central auditory system.

Another potential explanation for the weak, non-significant correlation is that contralateral suppression of the 40-Hz ASSR represents an effect such as central masking (Zwislocki, 1972), which is argued by Maki *et al.* (2009) to not involve the MOC system. However, even the role of the MOC in central masking is controversial. Some psychophysical work in humans and in animals supports the involvement of the MOC in central masking (Smith *et al.*, 2000; Aronoff *et al.*, 2015), but electrophysiologic work in animals with selective blockade of MOC efferents suggests that the MOC is not involved in central masking (Aran *et al.*, 2000). More work is needed to determine the extent to which the MOC contributes to contralateral suppression of the ASSR before it can be used as a metric of MOC activity.

D. Potential limitations

A click rate of 39.0625/s was utilized in the current study in order to elicit ASSRs close to 40 Hz and also to elicit TEOAEs. However, this click rate likely elicited the ipsilateral MOC pathway (Boothalingam and Purcell, 2015). In this case, the size of the magnitude of change that can be detected between the *no CAS* and *CAS* conditions would be reduced, because there would be partial MOC activation in the *no CAS* condition (Guinan, 2006). However, if correct, ipsilateral MOC activation did not prevent the measurement of robust contralateral suppression seen in all subjects in this study. Additionally, no evidence of MEMR activation due to CAS was uncovered in any subject, but it cannot be determined from the current measurements whether the click stimuli themselves elicited the MEMR in both the *no CAS* and *CAS* conditions.

Increasing the click rate to measure 80-Hz ASSRs would increase the likelihood of ipsilateral MOC activation and MEMR activation (Boothalingam and Purcell, 2015), so it may not be feasible to use a click-evoked paradigm as in the current study to assess the 80-Hz ASSR. A click rate slower than 40 Hz [e.g., 20 Hz, where robust contralateral suppression of ASSRs can be obtained (Usubuchi *et al.*, 2014)] could be used to avoid ipsilateral MOC activation and MEMR while still allowing for concurrent measurement of TEOAEs and of ASSRs. However, relative to the 40-Hz ASSR, amplitudes of ASSRs <40 Hz are lower and the noise floors are higher (Picton *et al.*, 2003), which could require longer data-collection times than those seen in the current study. It may be that different stimulus and recording paradigms from those used here are needed to assess contralateral suppression with ASSRs less than or greater than 40 Hz.

The present study implemented a visual attention task designed to minimize drifts in attention across the recording period. It has been demonstrated that visual attention by itself can modulate OAE and ASSR amplitudes in the absence of CAS (e.g., Puel *et al.*, 1988; Wittekindt *et al.*, 2014), presumably due to corticofugal activity involving the MOC. Therefore, engaging subjects in the current visual attention task may have elicited MOC activity in addition to the MOC activity caused by the CAS. As mentioned previously, subjects were engaged in the task during both conditions with and without CAS, so attention-based MOC effects should be similar between conditions and any response amplitude differences between conditions should therefore have been due primarily to MOC activation caused by CAS. Additionally, the effects of visual attention (approximately 0.2 dB; Wittekindt *et al.*, 2014) would be smaller than the effects observed in the present study. Furthermore, de Boer and Thornton (2007) found no significant difference in contralateral suppression of TEOAEs in a condition with CAS and passive listening relative to a condition with CAS and visual attention. Therefore, it is likely that the observed amplitude changes in this study were due primarily to CAS, with a smaller contribution from the visual attention task.

The concurrent measurement paradigm used in this study ensured that any drift in stimulus levels across time would impact both the TEOAEs and ASSRs. Additional *post hoc* analysis of stimulus stability, expressed as the maximum percent change in amplitude between the initial click and all remaining clicks after rejecting artifacts (Glattke and Robinette, 2007), showed high stability in all subjects (mean $= 92.1\%$, SD $= 3.1\%$, range $= 85.7\%$–96.6%). However, methods to reduce stimulus drift could be implemented as well. *Post hoc* detrending of stimulus levels is one method to reduce drift, but Goodman *et al.* (2013) found that detrending in most cases did not alter whether a TEOAE amplitude change was statistically significant, relative to no detrending. In the present study, stimulus levels were calibrated in the ear canal prior to each recording, but it is possible that periodic re-calibration of stimulus levels during recording (e.g., after a subject moves or swallows) could minimize drift and should be explored in future studies. In the present study, a single click stimulus level of 75 dB pSPL was used to elicit TEOAEs and ASSRs. MOC activity has a stronger effect on responses to lower stimulus levels (Hood *et al.*, 1996) and thus a lower stimulus level may have shown larger CAS effects. Preliminary testing for this study showed that a click level of 65 dB pSPL did not elicit measurable ASSRs in some subjects, which could be a result of their age and/or hearing status (recall that mainly older adults, some with mild hearing loss, were tested in this study). Future research could incorporate measurements at multiple stimulus levels to compute "effective attenuation" (e.g., Collet *et al.*, 1990; Puria *et al.*, 1996; de Boer and Thornton, 2007; Lichtenhan *et al.*, 2016), which is the difference in stimulus level with versus without CAS that is needed to achieve the same TEOAE or ASSR magnitude. This is in contrast to the current study, in which the stimulus level was constant and the change in TEOAE and ASSR levels with versus without CAS was computed. Effective attenuation may be a more sensitive metric of MOC activity than contralateral suppression at a single stimulus level. For example, de Boer and Thornton (2007) found no significant effect of CAS on TEOAE levels measured at a single stimulus level, but found a significant

effect of CAS when the effect was expressed as effective attenuation. The current study has established that contralateral suppression of TEOAEs and of ASSRs can be measured simultaneously, laying the groundwork for future studies comparing parameters such as effective attenuation.

V. CONCLUSIONS

Contralateral suppression of TEOAEs and of ASSRs could be measured concurrently, usually with high test–retest reliability. The magnitude of contralateral suppression of ASSRs was nearly always greater than that of TEOAEs obtained at the same stimulus level. Contralateral suppression of TEOAEs and of ASSRs was not significantly correlated, suggesting that contralateral suppression of ASSRs may not serve as a valid substitute measure for contralateral suppression of TEOAEs in hearing-impaired ears. Future work is needed to determine the role of the MOC in contralateral suppression of ASSRs.

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