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Establishing Critical Differences in Ear-Canal Stimulus Amplitude for Detecting Middle Ear Muscle Reflex Activation During Olivocochlear Efferent Measurements

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KEYWORDS

Acoustic reflex; contralateral inhibition; MOC; olivocochlear efferent; otoacoustic emissions

ABSTRACT

Objective: Assessments of the medial olivocochlear reflex (MOCR) may have clinical utility. The MOCR is measured using contralateral inhibition of otoacoustic emissions but concurrent activation of the middle ear muscle reflex (MEMR) confounds test interpretation. MEMR activation can be detected using the change in ear-canal stimulus amplitude without versus with an MOCR elicitor. This study provides a description of how critical differences in ear-canal stimulus amplitude can be established.

Design: Clicks were presented in right ears without and with a contralateral MOCR elicitor. Ear-canal stimulus amplitudes were measured. Two measurements without an elicitor were used to develop critical differences. MEMR activation was considered present if the difference in ear-canal stimulus amplitude without versus with an elicitor exceeded the critical difference.

Study Sample: Forty-six normal-hearing adults (mean age = 23.4 years, 35 females) participated, with data from 44 participants included in the final analysis.

Results: Two participants exceeded the 95% critical difference. The 80%, 90%, and 99% critical differences are also reported for reference.

Conclusions: Results suggest that the contralateral elicitor can evoke the MEMR in a small number of participants. The methods described in this paper can be used for developing equipment- and clinic-specific critical differences for detecting MEMR activation.

Introduction

The auditory brainstem can exert control over outer hair cell motility via the medial olivocochlear (MOC) efferent system (reviewed in Guinan 2006; Lopez-Poveda 2018). MOC activation improves neural encoding of sounds in the presence of background noise (Winslow and Sachs 1987; Kawase et al. 1993) and reduces auditory damage due to high-intensity sound (Rajan 1988; Maison and Liberman 2000). Human studies suggest that the MOC contributes to the perception of speech in background noise (e.g., Giraud et al. 1997; Kumar and Vanaja 2004; Mishra and Lutman 2014; Mertes et al. 2019). Potential clinical applications of MOC assessments include determining individual susceptibility to noise-induced hearing loss (Maison and Liberman 2000), screening for auditory neuropathy spectrum disorder (Hood et al. 2003), and identifying the potential physiologic source of auditory complaints in clinical populations such as auditory processing disorder (Muchnik et al. 2004; Morlet et al. 2019), tinnitus (Riga et al. 2016), and hyperacusis (Wilson et al. 2017).

MOC activity can be assessed indirectly using otoacoustic emissions (OAEs), which are low-level sounds generated as a byproduct of outer hair cell motility (reviewed in Kemp 2002). OAE amplitudes are often compared when measured without versus with a contralateral elicitor noise to activate the MOC reflex (MOCR), where amplitude typically decreases in the presence of the contralateral elicitor (Collet et al. 1990). OAEs are a routine component of audiologic practice, suggesting that OAE-based assessments of the MOCR may be clinically feasible.

However, a complication of such measurements is that the contralateral elicitor can also simultaneously activate the middle ear muscle reflex (MEMR), which causes contraction of the stapedius muscle and thus alters the impedance of the middle ear (Møller 1962). MEMR activation can decrease OAE amplitudes much like the MOCR does, which complicates test interpretation

because the relative contribution of the MEMR versus the MOCR must be disentangled (for a detailed discussion, see Guinan et al. 2003; Marks and Siegel 2017).

Alternatively, avoidance of MEMR activation during the measurement ensures that changes in OAE amplitude caused by the contralateral elicitor are due to the MOCR. From both a clinical and research perspective, it is important to examine the contribution of the MOCR in isolation. A common method of detecting MEMR activation is to examine the change in OAE-evoking stimulus amplitude measured in the ear canal without versus with the contralateral elicitor (e.g., Abdala et al. 2013). Because the MEMR alters middle ear impedance, it has the ability to change the amplitude of the OAE-evoking stimulus that is reflected back to the ear canal microphone. In contrast, the MOCR alters outer hair cell function which has no effect on ear-canal stimulus amplitudes.

Most recent work has determined the presence of MEMR activation using a criterion change in ear-canal stimulus amplitude without versus with a contralateral elicitor. If the difference exceeds a specified amount, this is taken as evidence that the MEMR was activated by the contralateral elicitor (Abdala et al. 2013; Boothalingam and Purcell 2015; Lichtenhan et al. 2016; Bhatt 2017; Marks and Siegel 2017; Boothalingam et al. 2018; Mertes 2018). Many of these studies have used a criterion of 0.12 dB reported in Abdala et al. (2013) which was based on studies of wideband acoustic immittance measures of the MEMR (Feeney et al. 2003). It is of note that the 0.12 dB criteria originated from MOCR measurements using distortion-product OAEs (DPOAEs) for a contralateral elicitor level of 60 dB SPL, which may not be applicable to other OAE types and/or elicitor levels. Other studies have used statistical resampling procedures to identify significant changes in ear-canal stimulus amplitude for individual subjects (Goodman et al. 2013; Mertes & Goodman 2016; Lewis 2018).

An alternative method to detecting significant MEMR activation is to establish critical differences in ear-canal stimulus amplitude. The critical difference is the minimum amount of change in a measurement that is considered a true change and not due to random variation. The concept of the critical difference has related terms in the literature, including "minimum detectable change", "smallest detectable difference", and "reference range". Establishing the critical difference involves measuring test-retest variability and calculating cutoff values. Often, the cutoffs are computed using the standard error of measurement (SEM), described in more detail in the Methods section. As discussed in Reavis et al. (2013), an SEM approach has been utilized in the study of test-retest variability for a number of audiologic measures including otoacoustic emissions and MOCR assessments (Beattie et al. 2003; Keppler et al. 2010; Helleman and Dreschler 2012; Kumar et al. 2013). Additionally, an SEM approach has been implemented in hearing research for detecting differences in measurements including speech recognition (e.g., Wilson and McArdle 2007) and hearing aid outcome questionnaires (e.g., Smith et al. 2009).

Often, the goal of establishing critical differences is to determine when a change in an audiologic outcome is considered clinically significant, such as a decrease in OAE amplitude or word recognition due to progression of hearing loss. However, we can apply the same principles to the detection of MEMR activation. The ear-canal stimulus amplitude during an OAE measurement is expected to be stable during a measurement, provided there is no appreciable change due to factors such as probe slippage, environmental noise, or changes in middle ear pressure. In the presence of a contralateral elicitor, any change in stimulus amplitude that exceeds the critical difference can therefore be attributed to MEMR activation.

The purpose of this article is to provide a description of establishing critical differences in ear-canal stimulus amplitude which will serve as a guideline for establishing ones' own critical

differences using different equipment setups. A secondary interest was whether a brief measurement (<30 s) could reasonably detect MEMR activation, which could be useful for clinical assessments of the MOCR. In studies implementing bootstrap analyses, MOCR measurements were made over the course of several minutes, and MEMR activation was assessed afterwards (e.g., Mertes and Goodman 2016). It is possible that a shorter measurement of the MEMR itself could allow for faster detection in a clinical setting, which could provide guidance on how to proceed with the MOCR assessment.

Materials and methods

Participants

Participants were recruited from the University of Illinois at Urbana-Champaign campus. The research protocol was approved by the Institutional Review Board of the University of Illinois at Urbana-Champaign. Written informed consent was obtained from all participants. Participants were provided monetary compensation.

Forty-six individuals with normal hearing participated (11 males, 35 females, mean age = 23.4 years, standard deviation = 5.5 years). Participants were required to be right-handed and have no history of the following: hearing loss, vertigo, use of ototoxic medications, middle ear disease, severe and/or bothersome tinnitus, and noise exposure within the past 6 months. At the laboratory visit, eligible participants were required to have an unremarkable otoscopic examination, 226-Hz tympanograms within normal limits based on Mertes (2018) [tympanometric peak pressure: -100 to +50 daPa; ear canal volume: 0.6 to 2.5 cc; compliance: 0.2 to 1.8 mL], air-conduction thresholds ≤20 dB HL at octave frequencies from 250–8000 Hz, and measurable transient-evoked otoacoustic emissions (TEOAEs) from 1000 to 2000 Hz in the right ear. We defined "measurable"

as having a signal-to-noise ratio (SNR) of at least 6 dB and a reproducibility of at least 70% in response to 1250 sweeps of clicks presented at 65 dB peak SPL (pSPL) at a rate of 19.51/s (Mertes 2018).

Equipment

Testing was conducted in a single-walled sound-treated booth. Participants were seated in a recliner during testing and watched a silent, closed-captioned video of their choice on an iPad Air 2 tablet computer (Apple, Cupertino, CA). Measurements were conducted using an RZ6 I/O processor (Tucker-Davis Technologies, Alachua, FL) interfacing with a WS4 PC workstation (Tucker-Davis Technologies), an ER-10B+ probe microphone (Etymōtic Research, Elk Grove Village, IL) with +40 dB preamplifier gain, and ER-2 insert earphones (Etymōtic Research). Analyses were conducted using MATLAB (ver. 2018a, The MathWorks, Inc., Natick, MA) and SPSS (ver. 25.0.0.0, IBM Corp., Armonk, NY).

Measurement paradigm

The overall measurement paradigm follows that of previous investigations that incorporated TEOAE-based assessments of the MOCR (e.g., Hood et al. 1996; Mishra and Lutman 2014; Mertes 2018). This paradigm involves a series of clicks presented to the right ear without a contralateral elicitor (no-elicitor condition) to establish baseline TEOAE amplitudes, followed by a series of clicks presented to the right ear along with presentation of a contralateral elicitor for evoking the MOCR (elicitor condition), followed by another series of clicks to the right ear without a contralateral elicitor (a second no-elicitor condition) to establish short-term stability of TEOAE

amplitudes in the absence of the contralateral elicitor (note that the focus of this study was on ear-canal stimulus amplitudes).

The stimulus and recording parameters are based on our previous research for investigating the MOCR using TEOAEs (Mertes 2018). Broadband clicks for eliciting TEOAEs consisted of 40.96-μs pulses (electrical bandwidth = 0 to 24414 Hz) delivered at a rate of 19.51/s to avoid eliciting the ipsilateral MOCR (Boothalingam and Purcell 2015). Clicks were presented through ER-2 insert earphones attached to the ER-10B+ probe assembly. Clicks were presented to right ears at 65 dB pSPL. Immediately prior to the recording, click levels were calibrated in-situ to be within ±0.25 dB of the target level. The contralateral elicitor consisted of broadband Gaussian noise (electrical bandwidth = 0 to 24414 Hz) presented through ER-2 insert earphones to left ears at 60 dB SPL as calibrated in an AEC202 2-cc coupler (Larson Davis, Depew, NY). We chose to measure TEOAEs in right ears and present the contralateral elicitor in left ears because this configuration yields larger MOCR effects in right-handed individuals (Khalfa and Collet 1996). The TEOAE microphone recordings were sampled at a rate of 24414.1 Hz, highpass filtered using a second-order Butterworth filter with a cutoff frequency of 500 Hz, and stored to disk for offline analysis.

A schematic of the stimulus presentation is shown in Figure 1. For the first no-elicitor condition (*no elicitor 1*), a train of clicks was presented to the right ear for 8 s with no stimuli presented to the left ear for 8 s. This was followed by 0.5 s of silence in the right ear and 0.5 s of the contralateral elicitor to allow for the full onset of the MOCR prior to the next condition (Backus and Guinan 2006). The elicitor condition (*elicitor 1*) consisted of a train of clicks presented to the right ear for 8 s along with presentation of the contralateral elicitor in the left ear for 8 s. The elicitor condition was followed by 0.5 s of silence in both ears to allow for full offset of the MOCR

prior to the second no-elicitor condition (Backus and Guinan). Finally, the second no-elicitor condition (*no elicitor 2*) was presented and was identical to the first no-elicitor condition. Because of the interest in a rapid assessment of MEMR, this stimulus paradigm only included one measurement of these three elicitor conditions.

Data extraction

The recorded click stimuli in each elicitor condition were stored in separate matrices and analyzed offline in MATLAB. To isolate the click stimulus, recorded waveforms were time windowed with a rectangular window as in Mertes and Goodman (2016). The window was 1.36 ms in duration, starting 0.2 ms before the peak of the click stimulus and extending to 1.16 ms after the peak of the stimulus (example stimulus waveforms for one participant are shown in Fig. 2A). This time window was chosen to maximize the measured effect of the MEMR on the ear-canal stimulus amplitude, given the delay between stimulus presentation and activation of the MEMR (Feeney et al., 2017; Marks and Siegel, 2017).

We removed linear trends in each recorded waveform (e.g., due to probe slippage or changes in middle ear pressure) by applying the MATLAB function 'detrend.m'. Visual inspection of the stimulus waveforms before and after detrending demonstrated that the procedure performed as intended. An example of the detrended stimulus waveforms for one participant is shown in Figure 2B. It can be seen that detrending reduced the noise present in the recorded waveforms. Across all participants, detrending decreased the mean percentage of rejects by 0.59% and decreased the mean noise floor by 2.04 dB SPL relative to no detrending when collapsed across elicitor conditions. Although nonlinear trends such as a participant briefly swallowing during the measurement would not be removed by this procedure, such instances would presumably result in

high-amplitude responses that would be discarded by the artifact rejection procedure. Given the performance of the detrending procedure, we recommend that future work in this area consider implementing detrending to reduce the noise floor and reduce the number of sweeps identified as artifact.

Because the presence of high-amplitude artifacts could impact measured ear-canal stimulus amplitudes, we performed artifact rejection post-hoc based on methods described in Goodman et al. (2009). Stimulus waveforms with a root-mean-square (RMS) amplitude that exceeded 1.5 times the interquartile range across all recorded waveforms within a participant were discarded.

We quantified the ear-canal stimulus amplitudes as well as the SNR of the stimuli. Signal and noise floor waveforms were obtained using a two-buffer approach, where odd-numbered waveforms were stored in buffer A and even-numbered waveforms were stored in buffer B (Prieve et al. 1993). The signal was obtained as $\frac{(A+B)}{2}$ and the noise floor was obtained as $\frac{(A-B)}{2}$. The first and last 0.045 ms were ramped with a Hann window. The mean of the signal and noise floor waveforms was computed. For each participant, the RMS ear-canal stimulus amplitude (i.e., the signal) amplitude and RMS noise floor amplitude (both in dB SPL) were computed across the 1.36 ms time window. RMS amplitudes in each condition are shown for one participant in Figure 2B. For each elicitor condition, each participant contributed one signal amplitude and noise floor amplitude.

Data analysis

When assessing the MOCR, the data are often analyzed as the difference in TEOAE amplitude in the first no-elicitor condition and the elicitor condition. For this difference to be attributed to the MOCR (and not due to other factors such as probe drift), the magnitude of this difference should

exceed the magnitude of the difference in TEOAE amplitude between the first and second no-elicitor conditions. However, the current analysis differs because the focus is on the recorded ear-canal stimulus amplitudes obtained in the no-elicitor and elicitor conditions. Therefore, we do not report any MOCR data in this paper (MOCR data from a subset of participants are reported in Mertes 2018 and Mertes et al. 2019).

To calculate critical differences, we first computed the standard error of measurement as:

$$SEM = SD\sqrt{1 - r_{xx}} \quad (1),$$

where *SD* is the standard deviation across all ear-canal stimulus amplitudes in the two no-elicitor conditions and r_{xx} is the Pearson product-moment correlation coefficient for the ear-canal stimulus amplitudes in the two no-elicitor conditions. The 95% critical difference is defined as:

$$CD_{95} = \pm(1.96 \times SEM \times \sqrt{2}) \quad (2).$$

Other critical differences that have been utilized in the clinical literature include 80%, 90%, and 99% [in which case the value of 1.96 in Eq. 2 would be replaced with 1.282, 1.645, and 2.576, respectively (McMillan and Hanson 2014)]. We report all of these critical differences values for reference, with the caveat that the values will be influenced by the choice of stimulus, recording, and analysis parameters. For a given participant, the difference in ear-canal stimulus amplitude between the first no-elicitor and elicitor conditions is compared to the critical difference, and if this difference falls outside the critical difference, it suggests that MEMR activation was present due to the contralateral elicitor.

Results

Two participants had >10% of their stimulus waveforms rejected due to excessively noisy recordings. Therefore, the data from these two participants were excluded from the analysis based

on the inclusion criterion specified in Boothalingam and Purcell (2015). We did not attempt to retest these individuals for this study, but future studies should ensure that all participants are sufficiently quiet during the test session to maximize the number of data points included in the analysis. A Friedman nonparametric test was conducted to examine differences in percentage of rejects across elicitor conditions in the remaining participants. However, there was no statistically significant difference across conditions (*Mdn* = 0.641% in all conditions), $\chi^2(2) = 0.695$, $p = 0.706$.

It was first of interest to determine if any differences in ear-canal stimulus amplitude and noise floor across elicitor conditions were present at the group level. Ear-canal stimulus amplitudes and noise floors were normally distributed, as assessed with Shapiro-Wilk tests of normality ($p >$ 0.05 in all cases). Additionally, there were no outliers as assessed using median absolute deviation (MAD), where cases with a MAD exceeding 3.5 would be considered an outlier based on work by Helleman and Dreschler (2012). Mean RMS ear canal stimulus amplitudes (±1 SD) were 55.101 ± 0.968 dB SPL for *no elicitor 1*, 55.104 ± 0.971 dB SPL for *elicitor 1*, and 55.102 ± 0.969 dB SPL for *no elicitor 2*. A repeated measures analysis of variance (ANOVA) with Greenhouse-Geisser correction revealed no significant differences in ear-canal stimulus amplitudes across elicitor conditions, $F(1.299,55.850) = 0.195$, $p = 0.725$, partial $\eta 2 = 0.005$. Mean RMS noise floor amplitudes (±1 SD) were 6.174 ± 1.270 dB SPL for *no elicitor 1*, 6.230 ± 1.690 dB SPL for *elicitor 1*, and 6.128 ± 1.572 dB SPL for *no elicitor 2*. Mauchly's test for sphericity revealed that the assumption of sphericity was not violated, $\chi^2(2) = 2.064$, $p = 0.356$. A repeated measures ANOVA revealed no significant differences in noise floor amplitudes across elicitor conditions, $F(2,86) =$ 0.049, $p = 0.952$, partial $\eta 2 = 0.001$. Mean SNRs were 48.927 dB for *no elicitor 1*, 48.874 dB for *elicitor 1*, and 48.974 for *no elicitor 2* (no statistical test was run on SNRs due to lack of significant

247 difference in stimulus amplitudes and noise floors). These high SNRs allowed for the detection of
248 small changes in ear-canal stimulus amplitude (Goodman et al. 2013; Lewis 2018).

249 A scatter plot of amplitudes in the two no-elicitor conditions is shown in Figure 3. There
250 was a statistically significant correlation between amplitudes in the two no-elicitor conditions,
251 $r(42) = 0.999$, $p < 0.001$, indicating high short-term stability.

252 In computing the *SEM*, *SD* was 0.9626 and r_{xx} was 0.9998, resulting in an *SEM* of 0.0137.
253 The resulting critical differences are listed in Table 1. All critical differences were in hundredths
254 of a decibel, suggesting that small changes in ear-canal stimulus amplitude can be indicative of
255 MEMR activation.

256 After establishing the critical differences, the decibel difference in ear-canal stimulus
257 amplitude in the *no elicitor 1* and *elicitor 1* conditions were computed for each participant. If this
258 difference exceeded the critical difference, the result was interpreted as significant MEMR
259 activation. We considered changes in amplitude in both directions (i.e., amplitude increasing and
260 decreasing in the presence of the elicitor, respectively) as indicative of MEMR activation based
261 on work using wideband acoustic immittance to measure frequency effects of the MEMR (Feeney
262 et al. 2003).

263 The mean ear-canal stimulus amplitude difference between *no elicitor 1* and *elicitor 1* was
264 0.0028 ± 0.0403 dB (range = -0.0729 to 0.2368 dB). The number and percentage of participants
265 whose amplitude differences exceeded the critical difference are shown in the last column of Table
266 1. Figure 4 displays the amplitude difference sorted from low to high for all participants. The 95%
267 critical difference is shown by the dashed horizontal lines, where values falling outside these lines
268 indicated significant MEMR activation. Two participants exceeded the 95% critical difference.
269 One participant had an amplitude difference in the negative direction (i.e., ear-canal stimulus

amplitude decreased in the presence of the contralateral activator). It is of note that only one participant had an amplitude difference that exceeded the commonly-used criterion of 0.12 dB.

Discussion

Detection of the MEMR is critical for proper interpretation of OAE-based measurements of the MOCR. This study is the first to construct critical differences in ear-canal stimulus amplitude using an SEM approach. The critical differences reported in Table 1 are considerably smaller (more stringent) than a 0.12 dB criterion. Although there were no significant differences in mean ear-canal stimulus amplitude across conditions at the group level, two participants exceeded the 95% critical difference, suggesting probable MEMR activation. In contrast, only one participant demonstrated MEMR activation using the criterion of 0.12 dB. This suggests that the current method identified smaller amounts of MEMR activation than the typically used criterion for the click-based measurements as they were conducted in this sample of participants. We acknowledge that an MEMR detection approach that examines ear-canal stimulus amplitude changes is likely conservative because the ear-canal stimulus amplitudes have a higher SNR than the TEOAEs and because of the potential difference in frequency effects of the MEMR versus the MOCR (Liberman and Guinan 1998).

Additionally, it is of note that the 0.12 dB criterion originated from the work of Abdala et al. (2013) who conducted MOCR measurements using DPOAEs. Because DPOAEs involve tonal stimuli whereas TEOAEs involve transient stimuli, it is possible that different critical difference values would apply to the two types of stimuli. DPOAEs are typically elicited with higher-frequency stimuli relative to the frequencies contained within broadband clicks used for eliciting TEOAEs. The MEMR impacts middle ear function across a broad range of frequencies, but

activation of the MEMR causes the largest changes in wideband acoustic immittance below 1000 Hz (Feeney et al. 2017). The click stimuli used in this study may therefore exhibit smaller critical differences than tonal stimuli due to increased low-frequency energy.

The ear-canal stimulus amplitudes in the current study were normally distributed. This allowed us to compute the SEM. Nonparametric approaches are possible, which include using the percentiles from the sample distribution for determining the limits of variability. However, as discussed in McMillan and Hanson (2014), the sample size will need to be larger for a nonparametric approach. When developing one's own critical differences, the sample size and normality of the data are important factors to consider. Future work in our lab will include establishing critical differences using a larger number of participants and across a broader range of TEOAE-eliciting stimulus levels and contralateral elicitor levels.

An advantage of computing critical differences over using a single criterion value is that the stringency of the MEMR detection can be adjusted depending on the application and/or patient population. For example, some individuals with hyperacusis can present with abnormally low MEMR thresholds (Gordon 1986) which would need to be accounted for when assessing MOCR activity. Conversely, detecting susceptibility to noise-induced hearing loss for occupational or military applications may require less stringency in terms of differentiating MEMR from MOCR [see the comments of J. Guinan in the "Post-Talk Q&A" section of Goodman et al. (2018)].

Regarding our secondary interest of implementing a rapid (<30 s) measurement of MEMR activity, it remains to be seen whether this particular approach is clinically feasible. The SNRs of the click stimuli were high (mean of approximately 48 dB in all elicitor conditions), so further signal averaging does not appear to be necessary, at least for the 65 dB pSPL clicks used in this study. An advantage of the current methodology is that MEMR activation could be detected prior

316 to conducting a longer MOCR measurement, rather than examining the presence of MEMR post-
317 hoc after the MOCR measurement is conducted. However, it could be desirable to find the highest
318 elicitor level that does not activate the MEMR and then conduct the MOCR test at that intensity.
319 In such a case, the current methodology would need to be repeated with one or more elicitor
320 intensities, increasing test time. It should be noted that adjusting the elicitor intensity affects the
321 magnitude of the MOCR effect on OAEs (Hood et al. 1996) and would need to be taken into
322 account when comparing MOCR measurements across participants and studies. We presented the
323 contralateral elicitor at 60 dB SPL, a typical intensity for studies of the MOCR. If the goal is to
324 avoid MEMR activation in all participants, our data suggest that lower contralateral elicitor levels
325 may be required. Our finding of MEMR activation in some participants at 60 dB SPL is also
326 consistent with past work (Guinan et al. 2003).

327 We present the critical difference method as one potential tool for MEMR detection.
328 However, it is important to consider that other methods for detecting MEMR activation have also
329 been described recently. Goodman et al. (2013) computed bootstrapped confidence intervals for
330 detecting MEMR activation in individual participants. The ear-canal stimulus amplitudes from the
331 no-elicitor and elicitor conditions were pooled. Two random samples were drawn from this pool
332 and the difference was computed. This procedure was repeated 10,000 times to form a distribution
333 of resampled differences. If the actual mean difference in stimulus amplitude between conditions
334 exceeded the bootstrapped confidence intervals, MEMR activation was considered present. The
335 authors found that three participants out of 16 (18.75%) total showed significant MEMR activation
336 for contralateral white noise presented at 35 dB SL. This percentage is similar to that obtained
337 using the 80% critical difference in the current study. Because the critical difference is driven by
338 the results obtained in a sample of participants, a potential disadvantage is that it may be too

stringent or too lax in identifying MEMR activation in a particular individual, whereas the bootstrap method only considers the variability within the individual. However, by establishing a normative range of expected differences in ear-canal stimulus amplitude, this could be useful for identifying participants with excessively weak or strong MEMR activation.

For clinical purposes, a test of MEMR activation would ideally be brief. Future work should consider assessing if there is a difference in required data collection time for the critical difference method versus the bootstrapping method. Our method lasted approximately 30 s, whereas the bootstrapping methods used in Mertes and Goodman (2016) lasted 160 s and those used in Goodman et al. (2013) lasted 7.2 min. Of note, Goodman et al. (2013) used a nonlinear TEOAE extraction method which required 3 times the number of stimuli used in the linear extraction method used by Mertes and Goodman (2016) and in the current study. Additionally, the studies implementing bootstrapping analyzed MEMR activation from the MOCR recordings which required sufficient signal averaging to uncover the low-amplitude TEOAEs, whereas the current study used a brief measurement of the ear-canal stimuli which did not require as much signal averaging. An empirical investigation of the number of synchronous averages to include in a bootstrapping procedure to reliably detect MEMR activation should provide insight into the clinical feasibility of the different potential methods of detecting MEMR activation.

Marks and Siegel (2017) examined the difference waveform between the no-elicitor and elicitor conditions. For MEMR activation to be considered present, the SNR of this difference waveform had to exceed 5 dB within a time window that encompassed the stimulus. The authors found that participants did not exhibit significant MEMR activation until contralateral pink noise intensities reached 70 dB SPL or above. We only implemented one contralateral elicitor intensity of 60 dB SPL because this is commonly reported in the literature, so we could not assess the

MEMR threshold in our participants. The work of Goodman et al. (2013) and Marks and Siegel (2017) differed considerably in terms of methodology and participant samples from the current work, so comparisons of the relative sensitivity to MEMR activation should be interpreted with caution. A direct comparison of MEMR detection across methodologies in the same participant population appears warranted.

Marks and Siegel (2017) highlighted the important potential impact of synchronized spontaneous OAEs (SSOAEs) on measurements of MEMR activation. SSOAEs are similar to TEOAEs because they are both evoked by transient stimuli, but the SSOAEs persist for longer than TEOAEs (Wable and Collet 1994). If SSOAEs are of sufficient amplitude and are inhibited by the MOCR, this could be exhibited as a change in ear-canal stimulus amplitude even in the absence of an MEMR effect on the stimulus (see Supplemental Material 1 for further analysis and discussion; http://tandfonline.com/doi/suppl). The current study did not account for the MOCR effect on SSOAEs, so more work is needed to understand how SSOAEs can impact the establishment of critical differences in ear-canal stimulus amplitude.

We examined changes in the RMS amplitude of the click stimulus obtained in the time domain. However, this quantification did not allow for an examination of the effects across frequency. Feeney et al. (2003) have shown that the MEMR can cause increases in ear-canal reflectance below 1000 Hz which could cause an increase in ear-canal stimulus amplitude. However, above 1000 Hz, decreases in reflectance can occur which could cause decreases in ear-canal stimulus amplitude. Boothalingam and Purcell (2015) noted that these increases and decreases in stimulus pressure may cancel out if only examining the total ear-canal pressure, as was done in the current study. Goodman et al. (2018) used measurements of wideband reflectance to detect MEMR activation across different frequency bands, but they reported that there was

considerable inter-subject variability in terms of the patterns. The frequency-dependent effects of the MEMR on ear-canal stimulus amplitudes requires further investigation. However, this method introduces the complication of how to quantify the change in amplitude across frequency due to the large number of frequencies involved and due to the possibility of both increases and decreases in amplitude. A future direction of our research group is to incorporate wideband acoustic immittance methods (e.g., Feeney et al. 2017; Keefe et al. 2017; Goodman et al. 2018) to verify if the MOCR elicitor activates the MEMR. Such measurements would provide more precise identification of MEMR activation during measurements of the MOCR to enhance interpretation of the results, which is crucial for clinical implementation of MOCR measurements.

The methods to compute critical differences described in this paper can be implemented by others to develop their own normative ranges. It is crucial to note that the critical difference values will depend upon a number of factors, including instrumentation, stimulus and recording parameters, and characteristics of the participants. Therefore, the critical differences reported in this paper (Table 1) should not be interpreted as the sole critical difference value to apply in any context, but they will serve as a point of reference. Determining the critical differences is an important step to implementing interpretable OAE-based tests of the MOCR for research and clinical practice.

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2019). The current study included data from additional participants and represents a new application of the data.

Disclosure statement

No potential conflicts of interest were reported by the author.

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572 **Figure Captions**

573 **Figure 1.** Block diagram of the stimulus presentation across time. Black and gray boxes represent
574 stimuli presented to the right and left ears, respectively. Solid boxes represent the time periods that
575 comprised each test condition, while dashed boxes represent the time periods for the onset and
576 offset of the MOCR that were not included in the analysis.

577

578 **Figure 2.** Example data from one representative participant. Panel A: Recorded ear-canal stimulus
579 waveforms without detrending are shown. Gray tracings represent individual stimulus waveforms
580 in the *no elicitor 1* condition (for visual clarity, waveforms from the other conditions are not
581 shown). The thick black tracing represents the mean waveform. Time zero on the x-axis is shown
582 relative to the peak of the stimulus. Panel B: Recorded ear-canal stimulus waveforms are shown
583 after the detrending was applied. Panel C: RMS ear-canal stimulus amplitudes in each elicitor
584 condition. Error bars represent 1 SD.

585

586 **Figure 3.** Scatter plot of RMS ear-canal stimulus amplitudes in the two *no-elicitor* conditions.
587 Circles are individual data points (n = 44). The line represents a 1:1 correspondence between
588 amplitudes in each condition.

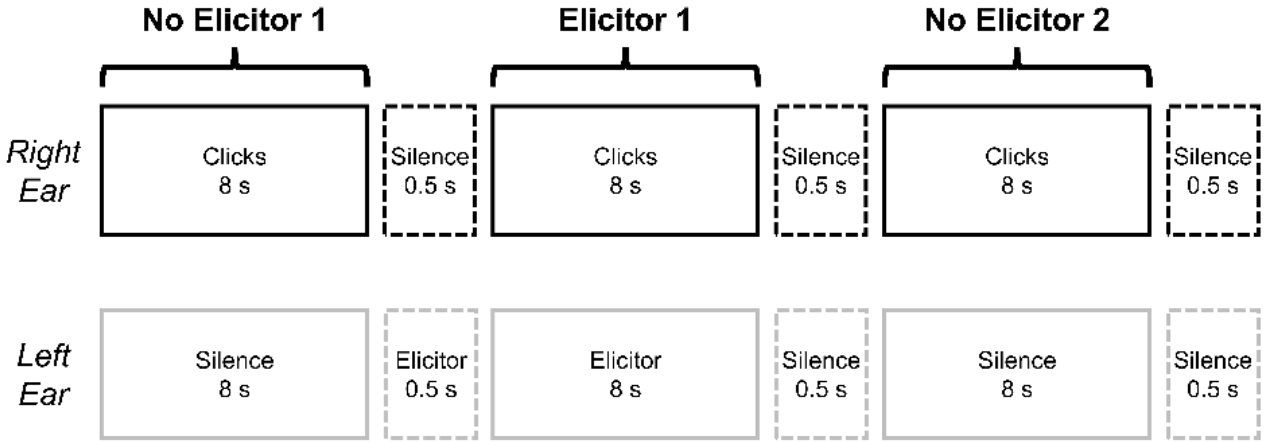
589

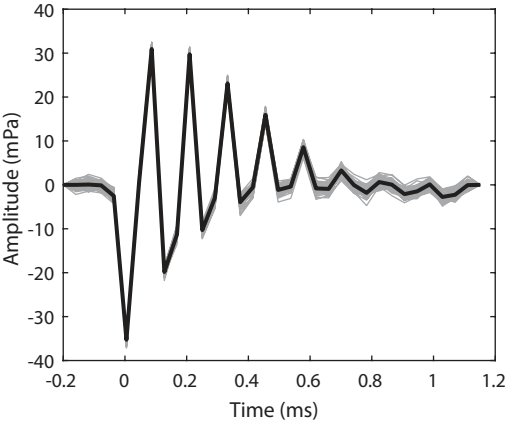
590 **Figure 4.** Differences in ear-canal stimulus amplitude between *no elicitor 1* and *elicitor 1*
591 conditions for all participants. The dashed lines represent the 95% critical difference. Circles
592 represent individual participant data sorted from low to high. Unfilled circles are results that did
593 not exceed the 95% critical difference (n = 42) and filled circles represent results that exceeded
594 the 95% critical difference (n = 2).

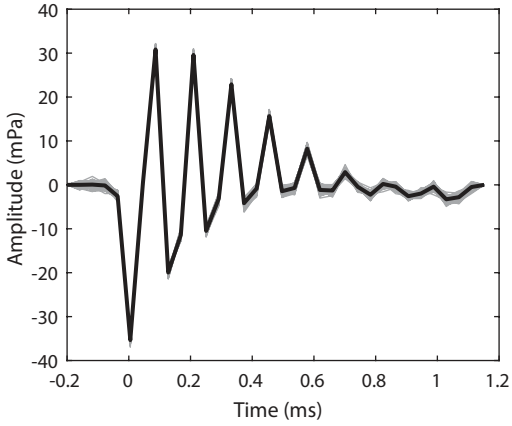
595 **Table 1**. Critical differences in ear-canal stimulus amplitude. The last column displays the number
596 of participants exhibiting probable MEMR (exceeding the critical difference), with the percentage
597 of participants shown in parentheses.

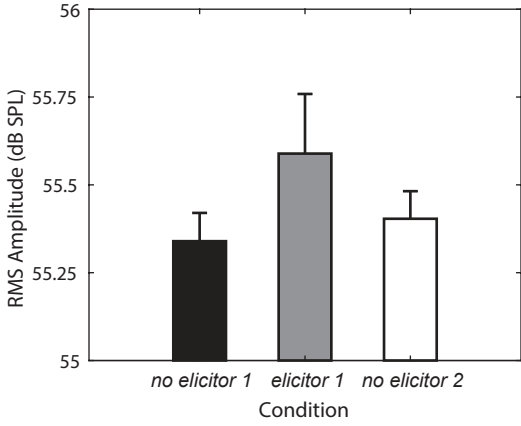
Critical Difference (%)	*Cutoff Values (dB)*	*Cases of Probable MEMR*
80	±0.0249	8 (18.18%)
90	±0.0320	4 (9.09%)
95	±0.0381	2 (4.55%)
99	±0.0500	2 (4.55%)

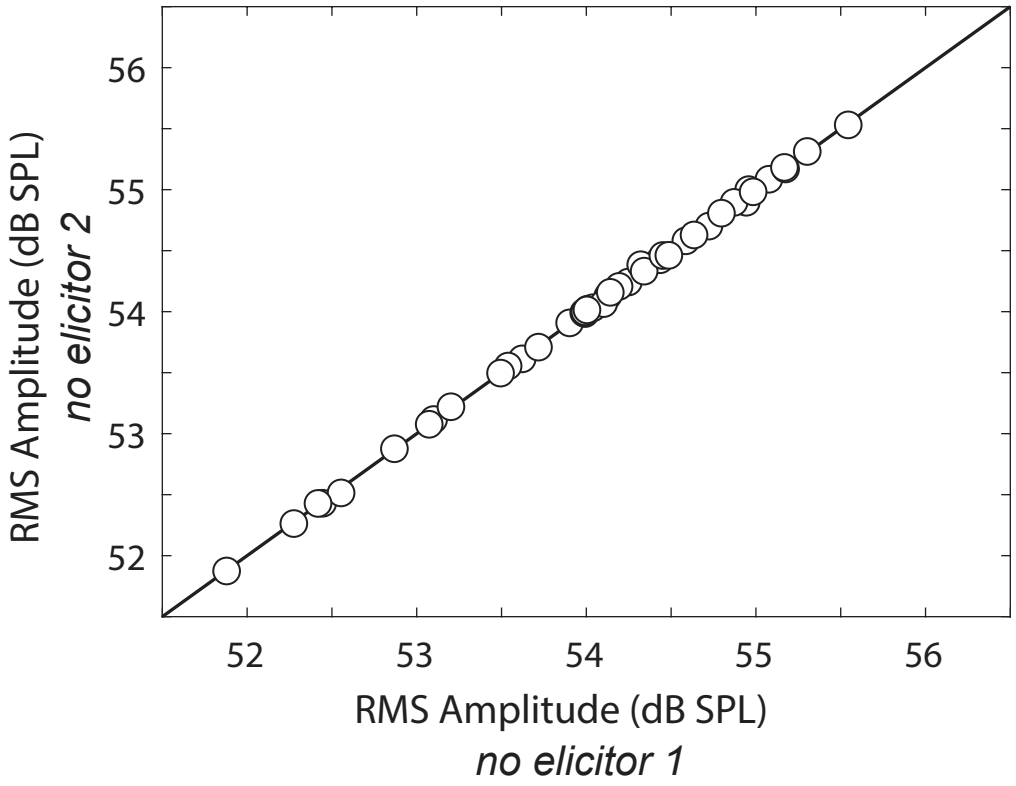
598

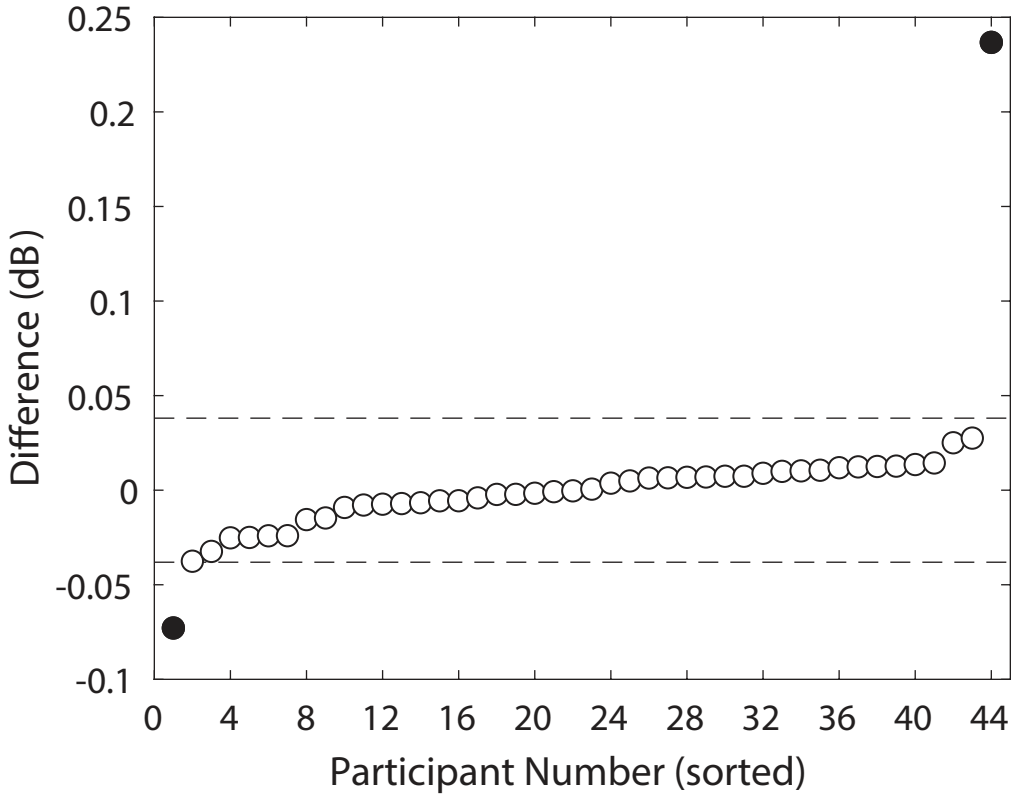

No Elicitor 1
Elicitor 1
No Elicitor 2
Right Ear
Clicks 8 s
Silence 0.5 s
Clicks 8 s
Silence 0.5 s
Clicks 8 s
Silence 0.5 s
Left Ear
Silence 8 s
Elicitor 0.5 s
Elicitor 8 s
Silence 0.5 s
Silence 8 s
Silence 0.5 s


Amplitude (mPa)
Time (ms)


Amplitude (mPa)
Time (ms)


RMS Amplitude (dB SPL)
no elicitor 1
elicitor 1
no elicitor 2
Condition


RMS Amplitude (dB SPL)
no elicitor 2
56
55
54
53
52
52
53
54
55
56
RMS Amplitude (dB SPL)
no elicitor 1


0.25
0.2
0.15
0.1
0.05
0
-0.05
-0.1
Difference (dB)
0
4
8
12
16
20
24
28
32
36
40
44
Participant Number (sorted)

Supplemental Material 1: Analysis of Synchronous Spontaneous Otoacoustic Emissions

The presence of synchronous spontaneous otoacoustic emissions (SSOAEs) was investigated using methods adapted from Mertes and Goodman (2016). SSOAEs were obtained from the transient-evoked otoacoustic emission (TEOAE) screening procedure described in the Methods (the short duration of the middle ear muscle reflex measurement did not allow for sufficient signal averaging to detect SSOAEs). SSOAEs were analyzed in the time window from 34 to 44 ms (relative to the location of the stimulus peak) because this window would not contain TEOAEs (Sisto and Moleti 2007). Waveforms were band pass filtered from 1000 to 4000 Hz using a Hann-window-based finite impulse response filter with a filter order of 128. The first and last 1-ms were ramped on and off with a raised-cosine ramp. Artifact rejection and comuptatuion of the root-mean-square signal and noise floor amplitudes were performed as described in the Methods. SSOAEs were considered present if the signal-to-noise ratio exceeded 6 dB.

Results revealed that 34 of 44 participants (77.27%) had present SSOAEs. This prevalence is consistent with that reported by Sisto et al. (2001), but differs from other reports (Jedrzejczak et al. 2008; Mertes and Goodman 2016; Lewis 2018). These discrepancies may be due to a combination of differences in stimuli, analysis, and participant characteristics. Of the 34 participants with present SSOAEs, the mean amplitude ±1 SD was 3.579 ± 5.773 dB SPL (range = −5.505 to 16.590 dB SPL).

The potential influence of SSOAEs on the middle ear muscle reflex (MEMR) results was examined through the scatter plot shown in Figure 1. Ear-canal stimulus amplitude differences are plotted against SSOAE amplitude. The SSOAE amplitude is shown for participants with present SSOAEs as well as absent SSOAEs to look for any qualitative differences between the two groups.

Visual inspection revealed no apparent relationship between the size of the difference in ear-canal stimulus amplitude and the SSOAE amplitude. This observation was confirmed by lack of a significant correlation, $r(42) = -0.129$, $p = 0.403$. Participants with absent SSOAEs showed a smaller range of difference values compared to those with present SSOAEs, but this may be due to the smaller number of participants with absent SSOAEs. The participant with the largest difference value (0.237 dB) that fell outside the 95% critical difference had an SSOAE amplitude that was on the lower end of the distribution of SSOAE amplitudes (−1.738 dB SPL, below the 25th percentile), suggesting that SSOAEs did not contribute appreciably to the difference in ear-canal stimulus amplitude. Conversely, the other participant with a difference value (−0.073 dB) falling outside the 95% cirtical difference had an SSOAE amplitude that was on the higher end of the distribution of SSOAE amplitudes (11.130 dB SPL, above the 75th percentile). This could suggest an influence of SSOAEs on the measured difference in ear-canal stimulus amplitude in this participant, although it is of note that other participants with SSOAEs of a similar amplitude did not exceed the 95% critical difference.

One factor we cannot account for in this analysis is the amount of medial olivocochlear reflex (MOCR) inhibition of the SSOAE (recall that the TEOAE screening data were analyzed for SSOAEs, which did not include a contralateral elicitor). If a large-amplitude SSOAE was sufficiently inhibited by the MOCR and was out of phase with the stimulus, this interaction could exhibit as a change in ear-canal stimulus amplitude even if there were no MEMR activation. The following equation illsturates the potential impact of SSOAEs. Equation 1 computes the difference value that would result from an interaction of the stimulus amplitude and an SSOAE that is inhibited by the MOCR:

$$\delta_{stim} = 20\ \log_{10}[(A_{stim} + (A_{ssoae} \times A_{moc})) \,/\, (A_{stim} + A_{ssoae})] \qquad (1),$$

where δ_{stim} is the estimated change in ear-canal stimulus amplitude in dB, A_{stim} is the RMS amplitude of the ear-canal stimulus in Pascals, A_{ssoae} is the RMS amplitude of the SSOAE in Pascals, and A_{moc} is the amplitude of MOCR inhibition of the SSOAE in linear units. For the aforementioned participant with a difference value of −0.073 dB and an SSOAE amplitude of 11.130 dB SPL, if we use an A_{stim} of 55 dB SPL and a reasonable value of A_{moc} of 0.707 (3 dB inhibition), the resulting δ_{stim} is −0.016 dB. This value is smaller than the participant's actual difference value, and δ_{stim} did not exceed the 95% critical difference. This suggests a lack of effect of SSOAEs on the results for this participant. Conversely, for the participant with the largest SSOAE amplitude (16.590 dB SPL), if we again use an A_{moc} of 0.707, δ_{stim} is −0.030 which exceeds the participant's actual difference value of −0.024 dB but does not exceed the 95% critical difference. In this participant, it could suggest that the value of A_{moc} overestimated the actual MOCR effect and/or that the inhibited SSOAE is not completely out of phase with the stimulus waveform.

Because no measurement of MOCR inhibition of the SSOAEs was obtained in the current study, these estimated effects of SSOAEs remain speculative. It appears that very large-amplitude SSOAEs may potentially impact the measured change in ear-canal stimulus amplitude, but only if the size of MOCR inhibition is substantially large. Further work is needed, but we recommend that future work include the analysis of SSOAEs and the MOCR effect on SSOAEs when developing critical differences.

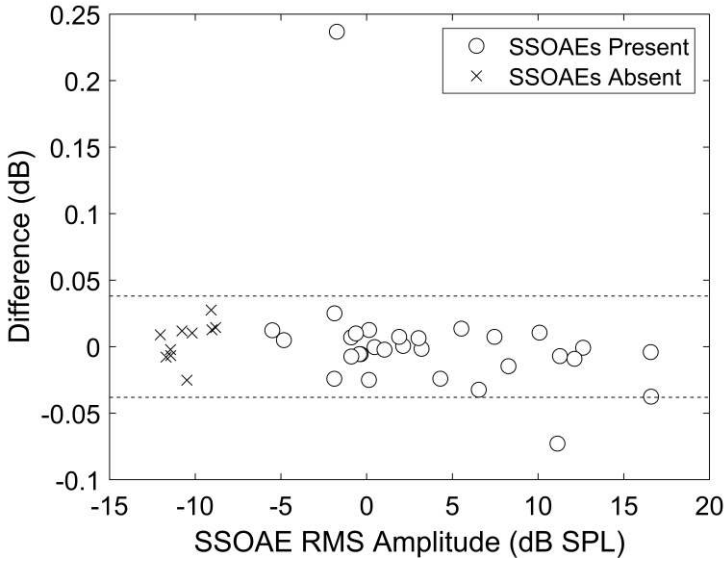


Figure 1. Differences in ear-canal stimulus amplitude (*no elicitor 1* versus *elicitor 1*) as a function of SSOAE amplitude. Open circles represent participants with present SSOAEs and x symbols represent participants with absent SSOAEs. The dashed horizontal lines represent the 95% critical difference.

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