Research Article

Stability of the Medial Olivocochlear Reflex as Measured by Distortion Product Otoacoustic Emissions

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Purpose: The purpose of this study was to assess the repeatability of a fine-resolution, distortion product otoacoustic emission (DPOAE)-based assay of the medial olivocochlear (MOC) reflex in normal-hearing adults.

Method: Data were collected during 36 test sessions from 4 normal-hearing adults to assess short-term stability and 5 normal-hearing adults to assess long-term stability. DPOAE level and phase measurements were recorded with and without contralateral acoustic stimulation. MOC reflex indices were computed by (a) noting contralateral acoustic stimulation-induced changes in DPOAE level (both absolute and normalized) at fine-structure peaks, (b) recording the effect as a vector difference, and (c) separating DPOAE components and considering a component-specific metric.

Results: Analyses indicated good repeatability of all indices of the MOC reflex in most frequency ranges. Short- and long-term repeatability were generally comparable. Indices normalized to a subject's own baseline fared best, showing strong short- and long-term stability across all frequency intervals.

Conclusions: These results suggest that fine-resolution DPOAE-based measures of the MOC reflex measured at strategic frequencies are stable, and natural variance from day-to-day or week-to-week durations is small enough to detect between-group differences and possibly to monitor intervention-related success. However, this is an empirical question that must be directly tested to confirm its utility.

The medial olivocochlear (MOC) tract courses from the midbrainstem level to innervate the outer hair cells of the cochlea. When activated, the MOC system hyperpolarizes the outer hair cells, thereby reducing gain of the cochlear amplifier and broadening cochlear filters (Fex, 1962; Francis & Guinan, 2010; Guinan, 2006). MOC effects have been linked to enhanced listening in noise and protection from acoustic trauma (Froehlich, Collet, & Morgon, 1993; Giard, Collet, Bouchet, & Pernier, 1994; Giraud et al., 1997; Kumar & Vanaja, 2004; Maison & Liberman, 2000). These effects can be modulated by attention and are task dependent (de Boer & Thornton, 2007; Froehlich et al., 1993; Maison, Micheyl, & Collet, 2001; Meric, Micheyl, & Collet, 1996).

In humans, the MOC reflex can be assessed with otoacoustic emissions (OAEs). Contralateral broadband noise effectively activates the MOC-mediated feedback loop, whereas OAE measurements provide evidence of altered cochlear output associated with this activation (for reviews, Guinan, 2006, 2010). The MOC effect can be evoked by ipsilateral, contralateral, or binaural noise. In this article, we focus on the contralateral MOC reflex. Distortion product otoacoustic emissions (DPOAEs) have been recorded at fine-frequency intervals with contralateral broadband noise in order to assay MOC activity in humans (Abdala, Mishra, & Williams, 2009; Deeter, Abel, Calandruccio, & Dhar, 2009; Henin, Thompson, Abdelrazeq, & Long, 2011). The DPOAE is a mixed emission comprising at least two components: *distortion* (generated at the overlap of primary tone frequencies, f_1 and f_2) and *reflection*, produced at the f_{dp} ($2f_1 - f_2$) place (Kim, 1980; Knight & Kemp, 2000; Shera & Guinan, 1999; Talmadge, Long, Tubis, & Dhar, 1999). The vector combination of these components in the ear canal gives rise to oscillations in DPOAE phase and level; these oscillations are called *DPOAE fine structure*. Notably, phase interference between distortion and reflection components can confound DPOAE-based measures of the MOC reflex, sometimes creating artifactual

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instances of enhancement (Abdala et al., 2009; Abdala, Mishra, & Garinis, 2013; Deeter et al., 2009).

There has been continuous interest in extending the application of OAE-based MOC measurements for clinical purposes, and effective application to individual subjects is emerging (Goodman, Mertes, Lewis, & Weissbeck, 2013). Groups of subjects with auditory disorders have been successfully separated using an MOC reflex metric (e.g., Hood, Berlin, Bordelon, & Rose, 2003; Muchnik et al., 2004); whether it can detect any one clinical patient with putative MOC impairment and associated perceptual deficits is not clear.

Measurement of the MOC reflex may prove to be clinically useful in several applications: (a) in screening individuals for susceptibility to acoustic trauma, as a weakened MOC effect has been observed in laboratory animals that are preferentially susceptible to noise-induced damage (Maison & Liberman, 2000); (b) in detection of individuals whose auditory deficit involves difficulty with perception in noise (Giraud et al., 1997; Micheyl & Collet, 1996; Micheyl, Perrot, & Collet, 1997); and (c) as an index to monitor efficacy of auditory training (de Boer & Thornton, 2008; Vuillet, Magnan, Ecalle, Thai-Van, & Collet, 2007). Altered MOC inhibitions have been reported in individuals with auditory neuropathy (Starr, Picton, Sininger, Hood, & Berlin, 1996), auditory processing disorders (Muchnik et al., 2004; Sanches & Carvallo, 2006), autism (Khalfa, Bruneau, et al., 2001), temporal lobe epilepsy (Khalfa, Bougeard, et al., 2001), learning disability (Garinis, Glattke, & Cone-Wesson, 2008), and tinnitus (Ceranic, Prasher, Raglan, & Luxon, 1998). Likewise, enhanced functioning of the MOC system has been reported in musicians (Micheyl, Khalfa, Perrot, & Collet, 1997; Perrot & Collet, 2014). Many of these results should be interpreted cautiously because some of the methods were compromised or limited; for example, the OAEs had low (3-dB) signal-to-noise ratios (SNRs), component interference was not controlled, or the middle ear muscle reflexes were not adequately considered.

These emerging applications underscore the importance of defining the stability of the MOC reflex so as to facilitate its usage as a tool to monitor auditory function over time. Few studies have assessed the constancy of MOC effects across repeated sessions to define response reliability. Here, we focus on studies that used DPOAE-based methods.

A recent study found low to high test-retest reliability in DPOAE-based estimates of the MOC reflex, likely because DPOAE fine structure was not considered. Intra-session reliability coefficients ranged from 0.2 to 0.7, and intersession reliability ranged between 0.5 and 0.8 depending on the frequency (Kumar, Methi, & Avinash, 2013).

Wagner, Frey, Heppelmann, Plontke, and Zenner (2008) examined the repeatability of two DPOAE protocols in assessing MOC efferent activity during two independent sessions. In protocol A, they measured MOC effects using DPOAE input/output functions generated with L1 levels ranging from 20 to 60 dB SPL. In protocol B, they recorded MOC effects at a frequency corresponding to a valley or notch in DPOAE fine structure. The two test sessions were

separated by 5 to 6 days. Wagner et al. (2008) calculated MOC efferent activity as (a) the mean of level changes (negative and positive values combined) for each subject upon contralateral stimulation, (b) the mean of all level changes in absolute value irrespective of whether the MOC effect was a reduction or enhancement of OAE amplitude, and (c) the difference between the highest and lowest suppression value (range of suppression) for each subject. Their results suggest good repeatability for the two DPOAE protocols, with the exception of range of suppression in protocol A, and were consistent with their previous studies using similar methods (Wagner et al., 2005; Wagner, Heppelmann, Müller, Janssen, & Zenner, 2007).

Wagner et al.'s (2008) estimation of the MOC reflex, however, was compromised for at least two reasons. First, averaging both positive and negative values of the MOC reflex (i.e., OAE reduction and enhancement) produced by contralateral noise no doubt diluted the size of the MOC effect. Second and more importantly, the measurement of the MOC reflex at fine-structure dips is contraindicated as it introduces confounds. At fine-structure dips, the two DPOAE components (distortion and reflection) are out of phase. The out-of-phase cancellation between components is released by contralateral noise, producing an abrupt increase in DPOAE level. This level increase, sometimes termed enhancement, is primarily due to shifts in reflection component phase, which also produces frequency shifts in DPOAE fine structure (Abdala et al., 2009; Deeter et al., 2009; Henin et al., 2011). Thus, the MOC data collected at fine-structure peaks (mostly reductions in DPOAE level) differ significantly from the data at the notches (enhancements), but this is not due to differences in the MOC reflex. Wagner et al. (2008) measured the MOC reflex at the very frequencies in DPOAE fine structure that exacerbate the problem of component mixing.

When recording the MOC reflex with a mixed OAE, like the distortion product OAE, the problem of artifactual enhancement can be mitigated by carefully selecting the frequencies at which to measure the MOC reflex. Abdala et al. (2009) recorded changes in DPOAE only at fine-structure peaks, where the two DPOAE components combine in phase, and observed inhibition (vs. enhancement) in more than 90% of measures. In this same report, subjects were tested twice within the same session (Trials 1 and 2) to probe response reliability; no significant effects of trial on MOC reflex estimates were found. The mean difference in the DPOAE peak-based MOC reflex summed across all frequencies between the two trials was 0.37 dB.

Most research probing MOC effects on DPOAEs over approximately two decades (e.g., Kim, Frisina, & Frisina, 2002; Kumar et al., 2013; Puel & Rebillard, 1990) measured DPOAE with gross frequency resolution and overlooked the fine structure. Without due consideration of the fine structure, it is not possible to know whether the measurement data point is at a peak or a notch; different effects are observed at a peak (mostly reductions) and at a notch (enhancements). Further, component unmixing (i.e., separating the distortion and reflection components) is possible only with fine-structure data. Consequently, the interpretation of

MOC effects on DPOAEs is confounded by the interaction of the two components, each generated by different mechanisms with different phase characteristics (Kim, 1980; Knight & Kemp, 2000; Shera & Guinan, 1999), and each component is shown to be differentially sensitive to the MOC effects (Abdala et al., 2009; Deeter et al., 2009; Henin et al., 2011).

Recently, several novel metrics that consider the fine structure and OAE generation mechanisms have been proposed to consider these problems (Abdala et al., 2009; Deeter et al., 2009; Henin et al., 2011). First, the MOC reflex can be quantified by measuring the difference in DPOAE level with and without contralateral noise at fine-structure peaks (Abdala et al., 2009; Deeter et al., 2009). Measurements at the peak mostly avoid the effects of DPOAE enhancements. Additionally, the SNR is typically higher at the peak; higher SNR is critical for computing OAE differences (Backus, 2007; Goodman et al., 2013). Second, the difference in DPOAE level with and without contralateral noise (i.e., the MOC reflex) should be normalized to each subject's own baseline DPOAE amplitude. Since DPOAE amplitude varies significantly across frequency and subjects (even for normal-hearing subjects), normalizing the MOC reflex by the subject's own baseline amplitude helps reduce this variance (Abdala et al., 2013; Backus & Guinan, 2007). Third, vector differences consider both magnitude and phase of DPOAEs for estimating MOC effects (Abdala et al., 2013) and have shown reduced variability in MOC reflex measures (Henin et al., 2011). Henin et al. (2011) showed that the vector differences are higher in magnitude and less variable between four subjects when compared with MOC effects measured at peaks and across all data points. Finally, separating the DPOAE components allows one to examine the effects of MOC activation on both distortion and reflection components. This is important because the two components are mechanistically different and respond differently to contralateral noise. Reflection components show larger changes compared with distortion components (Abdala et al., 2013; Deeter et al., 2009; Henin et al., 2011). From an applied perspective, it may be that reflection emissions—such as the click-evoked OAE or stimulus frequency OAE—provide a more robust measure of the MOC reflex. However, the total DPOAE, which often offers better SNR, remains one alternative if the measurements are taken at peaks or as a vector difference.

The objective of the present study was to assess the short-term and long-term intrasubject reliability of several tests of the MOC reflex based on the total DPOAE. These tests considered current understanding about DPOAE generation mechanisms in their calculation and application and controlled for component interference between distortion and reflection components by measuring at DPOAE fine-structure peaks only. In addition, the MOC indices were normalized by individual baseline amplitude, and the tests considered efferent-induced changes in both DPOAE amplitude and phase. We also controlled for the possibility of middle ear muscle reflexes and their potential impact on MOC reflex estimates.

Method

Subjects

Data were collected during 36 test sessions from four normal-hearing young adults (two females, two males) for assessing short-term stability and from five normal-hearing young adults (four females, one male) for assessing long-term stability. The four ears assessing short-term stability were tested daily for 4 consecutive days ($4 \times 4 = 16$ sessions). The five ears included in the assessment of long-term stability were tested weekly for 4 weeks ($5 \times 4 = 20$). Only right ears were tested. Subjects aged between 22 and 31 years ($M = 27.6$ years) participated in this study. MOC reflex measurements were repeated over 4 consecutive days to assess short-term stability and for 4 consecutive weeks to assess long-term stability. The screening process consisted of otoscopy, pure-tone audiometry, tympanometry, measurement of acoustic reflex thresholds, and an OAE protocol described below. Subjects were screened for hearing thresholds ≤ 15 dB HL at octave frequencies between 0.25 and 8.00 kHz using a GSI 61 audiometer (Grason-Stadler, Eden Prairie, MN) and for normal middle ear function using a GSI Tymptstar (Grason-Stadler, Eden Prairie, MN). Normal middle ear function was defined as a type-A tympanogram with static compliance between 0.4 and 1.5 cm^3 and peak pressure within ± 150 daPa.

Wideband acoustic reflex thresholds were recorded using a research device (Wideband reflectance research system, Interacoustics, Denmark) via a maximum likelihood technique (Keefe, Fitzpatrick, Liu, Sanford, & Gorga, 2010). Only subjects with acoustic reflex thresholds > 65 dB SPL were included in the study so as to minimize the contribution of this reflex to the MOC effect. An initial screening DPOAE-gram was conducted to ensure the presence of DPOAEs. All tests were conducted at the House Research Institute (Los Angeles, CA) in a sound-attenuated Industrial Acoustics Corporation booth, where participants were seated in a padded reclining chair and were instructed to stay awake throughout the test. This study was approved by the St. Vincent Medical Center Institutional Review Board, and informed consents were signed by all subjects prior to their participation in the research.

Study Protocol

In addition to undergoing the auditory tests specified in the previous paragraph, subjects were screened during the first session for the presence of DPOAEs with adequate SNR (≥ 6 dB) across the frequency range (binned into one-third-octave intervals). The first of the DPOAE-based MOC reflex test sessions was conducted in the first session as well. In the subsequent three test sessions, only DPOAE measurements were gathered to calculate MOC reflexes. To control for potential experimental variations, the same size probe tip was used during all test sessions for a given subject, and the same experimenter tested all subjects in all test sessions. The participants were instructed to stay awake and as still as possible during the experiment. However, they were not

instructed to either attend to or ignore the acoustic signals presented during data collection; hence, attention was neither monitored nor manipulated.

DPOAE Measurements

The DPOAE data collection and analysis were conducted using a custom-designed protocol previously described in Abdala et al. (2013) and reviewed below.

Instrumentation and calibration. Signal generation and recordings were controlled by custom software (developed by C. Talmadge, modified by P. Luo) and run on an Apple Macintosh laptop computer (Apple Inc., Cupertino, CA) via a MOTU (Mark of the Unicorn, Cambridge, MA) 828 MK II audio device. DPOAE measurements in the subject's ear canal were performed using an ER-10B+ probe microphone system including ER-2 transducers (Etymotic Research, Elk Grove Village, IL). Primary tones, f_1 and f_2 , were swept across three octaves at 8 s/octave (total 24 s) for a total of six sweeps in each condition. DPOAE level and phase estimates were taken from the average of these six sweeps. DPOAE recordings were made for frequencies between 500 and 4000 Hz using stimulus levels of 65 (L_1) and 55 (L_2) dB SPL and a constant stimulus frequency ratio (f_2/f_1) of 1.22. The output of the ER-10B+ microphone was preamplified and then passed through an analog high-pass filter with a 300-Hz cutoff frequency before being digitized by the MOTU and stored on the laptop hard drive.

DPOAE level and phase estimates were made using a least-square-fit algorithm (Long, Talmadge, & Lee, 2008) at frequency intervals ranging smoothly with frequency from 2.2 Hz (at 500 Hz) to 17.4 Hz (at 4000 Hz). The noise floor was estimated after phase inverting every alternate sweep window. The ER-2 frequency response was equalized at the plane of the eardrum individually for each subject by recording the half-wave resonance in the ear canal from 0.2 to 20.0 kHz, estimating the depth of insertion, and then selecting the corresponding equalization filter to produce approximately flat frequency response at the tympanic membrane (Lee et al., 2012).

MOC reflex measurements. Broadband noise was used as contralateral acoustic stimulation (CAS) and was presented through an ER-2 insert transducer at 60 dB SPL. This level has been shown to be an effective elicitor of the MOC reflex in human adults (Guinan, 2006). The NoN (no-CAS) and CAS DPOAE conditions were interleaved throughout the test protocol in alternating pairs with 2-s intervals between sweeps, until six sweeps were collected in each condition. In the CAS condition, the noise was presented 1 s prior to the presentation of DPOAE primary tones.

DPOAE fine-structure data analyses. As an initial data inclusion criterion, a median of every three consecutive points in the average was calculated and compared with the noise estimate at the corresponding frequency; if the SNR was lower than 6 dB, the data point was not accepted. Average DPOAE SNR across all subjects and sessions was 27 dB at frequencies <1000 Hz and was 31 dB

at frequencies >1000 Hz. Fine-structure maxima were identified using an automatic algorithm described in Abdala, Dhar, and Mishra (2011) and then were visually inspected for any obvious classification errors. The phase was unwrapped by sequentially subtracting 360° from all data points. The $2\phi_1 - \phi_2$ phase—where ϕ_1 and ϕ_2 are phases of the f_1 and f_2 stimulus tones, respectively—was subtracted from the DPOAE phase.

DPOAE component separation. To separate the two components of DPOAE, an inverse fast Fourier transform (IFFT) was conducted on DPOAE recordings from each octave-wide frequency segment using a MATLAB-based analysis software package (Talmadge et al., 1999; modified by P. Luo). Distortion- and reflection-emission components were separated on the basis of their respective delays. During IFFT, DPOAE complex pressure measured in the frequency domain was multiplied by a moving Hanning window in overlapping 50-Hz steps. The length of the Hanning window ranged from 400 Hz at the lowest DPOAE frequency to 930 Hz at the highest. Impulse response functions were determined for each window, and rectangular time-domain filters were applied to each impulse response to extract the desired delay. The filtered windows of data were then transformed back to the frequency domain by fast Fourier transform, and the level and phase of the distortion and reflection components were reconstructed.

MOC Reflex Indices

The effect of CAS on ear canal DPOAE and on the separated DPOAE reflection component was examined. The following indices of the MOC effect were computed:

1. $\text{MOCR}_{\text{dB}} = L_{\text{dp}}^{\text{CAS}} - L_{\text{dp}}^{\text{NoN}}$, where L_{dp} is DPOAE level. For MOC reflex indices, we restricted ourselves to measuring reductions in level (here, termed *inhibition* and shown as negative values). Episodes of CAS-induced enhancement were eliminated. Evidence suggests different mechanistic origins for CAS-induced enhancement compared with reduction in DPOAE level (Abdala et al., 2009; Deeter et al., 2009; Henin et al., 2011). We implemented this analysis strategy in an attempt to disentangle true MOC effects from artifacts related to component mixing.
2. $\text{MOCR}_n = (|P_{\text{dp}}^{\text{NoN}}| - |P_{\text{dp}}^{\text{CAS}}|) / |P_{\text{dp}}^{\text{NoN}}|$, where $|P_{\text{dp}}|$ is DPOAE amplitude. MOCR_n was calculated at fine-structure peaks only and was reported as a fraction of the baseline amplitude.
3. $\text{MOCR}_{\text{Vn}} = |(P_{\text{dp}}^{\text{CAS}} - P_{\text{dp}}^{\text{NoN}})| / |P_{\text{dp}}^{\text{NoN}}|$, where $|P_{\text{dp}}|$ is a complex DPOAE vector. MOCR_{Vn} was calculated as the amplitude of the difference vector between NoN and CAS and was reported as a fraction of the baseline amplitude.
4. $\text{MOCR}_{\text{Dn}}, \text{MOCR}_{\text{Rn}} = (|P_{\text{D}}^{\text{NoN}}| - |P_{\text{D}}^{\text{CAS}}|) / |P_{\text{D}}^{\text{NoN}}|$ and $(|P_{\text{R}}^{\text{NoN}}| - |P_{\text{R}}^{\text{CAS}}|) / |P_{\text{R}}^{\text{NoN}}|$, where $|P_{\text{D}}|$ and $|P_{\text{R}}|$ represent distortion- and reflection-component amplitudes, respectively. MOCR_{Dn} and MOCR_{Rn} are reported as a fraction of the baseline amplitude.

The ear canal DPOAE and the separated distortion component were similar given our choice of stimulus parameters (i.e., moderate–high primary levels and $f_2/f_1 = 1.22$). The IFFT confirmed that the dominant contribution to the DPOAE mixture measured at the microphone was from the distortion component; for this reason, we investigated the stability of the reflection-component (MOCR_{Rn}) only.

Middle Ear Muscle Reflex

The middle ear muscle reflex (MEMR) was measured with an Interacoustics wideband reflectance system; it was evoked by contralateral stimulation, and the threshold was established with a maximum likelihood technique (Keefe et al., 2010). The objective of the maximum likelihood procedure is to measure the threshold as a function of a set of fixed reflex activator levels using a predefined set of model probability functions (reviewed in Keefe et al., 2010). This test is more sensitive than clinical estimates of the MEMR and yields 12- to 14-dB lower acoustic thresholds, on average, for 1000- and 2000-Hz activators (Feeney, Keefe, & Marryott, 2003). The mean contralateral acoustic reflex threshold estimated from wideband acoustic reflex measurements ranged from 65 to 75 dB SPL across subjects. This is 5 to 15 dB above the CAS level (60 dB SPL) used to activate the contralateral MOC effect. These findings indicate that the MEMR was not activated during presentation of CAS at 60 dB SPL in the tested subjects.

Statistical Analyses

Short- and long-term stability of the measurements were examined separately. The data were inspected for normal distribution. Two analyses were applied to each of four MOC metrics to assess their test–retest reliability:

1. The 95% confidence intervals (CIs) of the mean were calculated within subjects across sessions to establish the natural intrasubject distribution of scores within any one individual over repeated sessions.
2. The Cronbach reliability coefficient (α) provides similar information as Pearson correlations, but the coefficient is standardized by the average variance. The reliability coefficient was calculated according to the equation

$$\alpha = \frac{(n \times c)}{v + (n - 1)c},$$

where n is the number of test sessions, c is the average intertest covariance among test sessions, and v is the average variance. A value of .70 to .95 shows good reliability (Tavakol & Dennick, 2011). Data points that were present for at least three out of four test sessions were included in computing the Cronbach's alpha. For DPOAE-based metrics, peaks in fine structure were labeled categorically and sequentially as $P_n \dots$. Cronbach's alpha values were calculated for Peaks P1 through P7 for ear canal DPOAE data.

Figure 1. Grand mean (thick line) and individual (thin lines) signal-to-noise ratios (SNRs) as a function of frequency. Individual SNRs represent the averaged SNR from all test sessions. Frequency was binned into one-third-octave intervals with center frequencies of 561 Hz, 707 Hz, 891 Hz, 1122 Hz, 1414 Hz, 2244 Hz, 2828 Hz, and 3563 Hz. DPOAE = distortion product otoacoustic emission.

Results

DPOAE SNR

Figure 1 shows the mean DPOAE SNRs calculated by subtracting noise floor estimates from DPOAE level estimates in one-third-octave intervals for all subjects. Center frequencies for one-third-band octaves were 561 Hz, 707 Hz, 891 Hz, 1122 Hz, 1414 Hz, 1791 Hz, 2244 Hz, 2828 Hz, and 3563 Hz. The mean SNR values include all available data points (at both minima and maxima). The DPOAE MOC reflex was measured at maxima only; if only maxima were to be considered in these calculations, the SNR would be substantially higher. To obtain reliable data from a variable calculated as a difference score, as is the MOC reflex, the SNR of each independent measure must be high enough that the difference itself demonstrates sufficient noise immunity. The robust DPOAE SNR values shown in Figure 1 suggest that MOC reflex estimates were not adversely affected by the noise floor.

DPOAE Fine-Structure Peaks

Figure 2 shows representative examples of short- and long-term DPOAE recordings in NoN and CAS conditions. As noted, the DPOAE fine-structure morphology is similar across test sessions, but more important to our research question, the differences between solid and dashed lines (i.e., the MOC reflex estimates) also appear to be similar across test sessions. An MOC reflex measurement at a given fine-structure peak was included for reliability coefficient analysis if it was present for at least three of the four test sessions. As the pattern of fine structure is idiosyncratic, the total number of fine-structure peaks differed among subjects and ranged from five to 12. For group data analysis, peaks were categorically labeled

Figure 2. The left panel displays distortion product otoacoustic emission (DPOAE) fine-structure data recorded with no contralateral acoustic stimulation (NoN) and with contralateral acoustic stimulation (CAS; 60 dB SPL) for one representative subject tested in four daily sessions (short-term stability). The right panel displays corresponding DPOAE fine-structure data for the same subject recorded weekly for 4 weeks (long-term stability).

P_n . . . , representing sequential maxima, irrespective of their actual frequency value. Hence, P1 was not centered at the same frequency for each individual subject, for example. However, because peaks were numerically labeled from low to high frequency for all subjects, they generally represented similar frequency ranges; peaks within any given P category were within one sixth an octave of one another at frequencies <2000 Hz and within one third an octave of one another for frequencies >2000 Hz. With the MOC reflex measured at fine-structure peaks, 96% of the short-term stability data points and 90% of the long-term data points showed decreases in DPOAE level (vs. enhancement) with the presentation of contralateral noise.

Short-Term Stability

The repeatability of four DPOAE measures— MOCR_{dB} , MOCR_n , MOCR_{Vn} , and component-specific MOCR_{Rn} —was assessed using 95% CIs and the Cronbach's coefficient (α).

DPOAE. Figure 3 shows the means and distribution of MOCR_{dB} and MOCR_n values for all peaks during Sessions A_s, B_s, C_s, and D_s in four subjects. The error bars represent the 95% CIs. Mean MOCR_{dB} combined across peaks ranged from -0.5 to -1.2 dB among subjects (negative values denoting inhibition/suppression) and was smallest in the high frequencies. This trend was noted in all subjects except Subject 2. The distribution of values (CIs) computed for each subject was relatively independent of frequency, as can be noted in Figure 3. The collective data across all four subjects show MOCR_{dB} results that vary with repeated testing by between approximately 0.03 and 0.47 dB for 95% of all measurements.

The Cronbach's reliability coefficients (α) for MOCR_{dB} are shown in Table 1 for both short- and long-term stability. This statistic assesses the relative constancy of the MOC reflex estimates within subjects and across time by testing the

association of MOC reflex values with one another. (Table 1 also presents the statistical results for MOCR_n and MOCR_{Vn} , which are discussed below.) These results suggest good short-term reliability of the MOCR_{dB} test for all peaks ($\alpha \geq .70$). Only P3 showed slightly reduced values, although α values ranged from .63 to .67. P3 includes DPOAE fine-structure peaks centered around 1460 Hz.

The MOCR_n index reported MOC reflex as a fraction of the baseline DPOAE level. The DPOAE was reduced by 0.05 to 0.12 on average (across frequency) across subjects. This can be thought of as 5% to 12% of the baseline amplitude. The largest fractional reduction was 0.16. The overall intrasubject variability in MOCR_n , as measured by 95% CIs, ranged from 0.002 to 0.048 in a relatively frequency-independent manner. The reliability coefficients for MOCR_n showed good reliability for all peaks ($\alpha \geq .7$). The MOCR_{Vn} reflex test captured CAS-induced changes in combined DPOAE phase and magnitude. The MOCR_{Vn} was reliable within subjects, showing a reliability coefficient of $\alpha \geq .7$, and for all peaks except P4 ($\alpha = .57$), which includes DPOAE values centered near 1596 Hz. It appears that DPOAE maxima in the 1450- to 1600-Hz range are least repeatable within subjects. Among the three MOC reflex tests derived from the DPOAE, only the MOCR_n showed good reliability for all peaks.

Component specific. Figure 4 shows reflection-component MOC reflex normalized by baseline amplitude and binned into one-third-octave intervals. The 95% CIs display the distribution of scores across four daily test sessions for each of five subjects. Consistent with previous studies (Abdala et al., 2009; Deeter et al., 2009; Henin et al., 2011), activation of the MOC reflex with CAS produced more robust effects on the DPOAE reflection component than the unseparated DPOAE (see Figure 3, upper panel) or presumably the distortion component. On average, CAS produced reductions in reflection component (summed across frequency) of

Figure 3. Mean medial olivocochlear reflex for each subject plotted as a function of distortion product otoacoustic emission (DPOAE) fine-structure peaks (P1 is centered at the lowest frequency, P1+n at progressively higher frequencies). Note that the total number of DPOAE fine-structure peaks is different for each subject. Error bars represent 95% confidence intervals. The lower panels display the normalized MOC reflex (MOCR_n) and the upper panels show the MOC reflex in dB (MOCR_{dB}).

between 0.07 and 0.19 of baseline amplitude. The strongest fractional reduction regarding baseline amplitude was 0.38. This is consistent with reports of the MOC reflex calculated from stimulus frequency OAEs, which are also reflection-type emissions (Backus & Guinan, 2007). The CIs ranged from 0.01 to 0.12 for the reflection-component MOC reflex test for within-subject session-to-session variability. The reliability coefficients for the component-specific MOCR_{Rn} showed good repeatability ($\alpha \geq .7$) across all one-third-octave frequency intervals (see Table 2).

Long-Term Stability

DPOAE. The mean MOCR_{dB} and MOCR_n are shown in Figure 5 as well as the 95% CIs depicting the intrasubject distribution of values across four weekly test sessions for five

subjects. Similar to corresponding short-term indices, mean MOCR_{dB} ranged from -0.5 to -1.3 dB among subjects, and intrasubject values varied across repeated sessions by 0.06 to 0.70 dB. The reliability coefficients (in Table 1) for repeated test sessions across a period of 1 month show good repeatability ($\alpha \geq .7$) for both MOCR_{dB} and MOCR_n tests at all peaks except P3 ($\alpha = .66$ for MOCR_{dB} and $\alpha = .63$ for MOCR_n). The reliability coefficients for the MOCR_{Vn} showed similar results for all peaks across the frequency range ($\alpha = .67$ for P3). Overall, the short- and long-term intrasubject reliability of the three DPOAE MOC reflex tests were comparable. It is interesting to note that MOCR_{Vn} at peak P4 showed better long-term than short-term repeatability, for unknown reasons.

Component specific. Figure 6 shows the mean MOCR_{Rn} and 95% CIs depicting the distribution of values across four

Table 1. Cronbach's coefficients for short- and long-term test sessions for ear canal distortion product otoacoustic emission–based medial olivocochlear reflex measurements.

Peaks	Short-term			Long-term		
	MOCR_{dB}	MOCR_n	MOCR_{Vn}	MOCR_{dB}	MOCR_n	MOCR_{Vn}
P1	.94	.91	.93	.84	.88	.86
P2	.96	.87	.97	.85	.88	.87
P3	.67	.71	.78	.66	.63	.67
P4	.81	.76	.57	.84	.92	.87
P5	.86	.84	.84	.84	.75	.76
P6	.81	.80	.83	.97	.96	.96
P7	.85	.86	.81	.71	.97	.96

Note. MOCR_{dB} = MOC reflex in dB; MOCR_n = normalized MOC reflex; MOCR_{Vn} = vector difference.

Figure 4. Mean reflection-component medial olivocochlear reflex (MOCR_{Rn}) for each subject plotted as a function of distortion product otoacoustic emission center frequency binned into one-third-octave intervals. Error bars represent 95% confidence intervals.

weekly test sessions for five subjects. The reflection component of the DPOAE (summed across frequency) was reduced by between 0.11 and 0.16 fraction of baseline amplitude. The largest reduction was 0.41. CIs indicate that 95% of values within any one subject across repeated tests varied by between 0.13 and 0.2. The distribution of values across test sessions did not vary notably as a function of frequency. The reliability coefficients of the MOCR_{Rn} index recorded across four weekly sessions indicated good reliability for all frequency intervals ($\alpha \geq .7$; see Table 2). Note that the Cronbach's alpha for the 3563-Hz frequency band for the long-term data could not be calculated, as the MOC reflex was not observed at this frequency band in at least three subjects.

Table 2. Cronbach's alpha coefficients for component-specific medial olivocochlear reflex for short- and long-term test sessions.

Center frequency (Hz)	Short-term	Long-term
707	.79	.93
891	.84	.85
1112	.82	.82
1414	.90	.83
1782	.87	.82
2245	.81	.82
2828	.86	.81
3563	.71	Not computed

Discussion

Stability of MOC Reflex Indices

We examined the intrasubject repeatability of a variety of indices gauging the MOC reflex: (a) a conventional index recorded as a simple change in DPOAE level produced by MOC activation (MOCR_{dB}), (b) a metric of this same level effect normalized to each subject's own baseline amplitude (MOCR_{n}), (c) a vector index that considered changes in both DPOAE amplitude and phase elicited by MOC activation (MOCR_{vn}), and (d) an index of changes in the IFFT-derived DPOAE reflection-component magnitude (MOCR_{Rn}). The reflection component was singled out because it is more affected by MOC activation than distortion (Abdala et al., 2009). We included the decibel-based MOC reflex test because it is perhaps most familiar in the early MOC literature and because the reader may have a more intuitive association with the decibel; however, we favor the normalized metric that considers baseline amplitude in its calculation because it showed slightly better repeatability and because it considers the magnitude of the baseline amplitude in its calculation. Other than the marginally enhanced repeatability with the normalized index, all three tests of DPOAE MOC reflex strength (decibel, normalized level, and vector difference) showed comparable short- and long-term stability. Of all peaks, the MOC reflex that was recorded around 1500 to 1600 Hz (P3 and P4)

Figure 5. Mean medial olivocochlear reflex for each subject plotted as a function of distortion product otoacoustic emission (DPOAE) fine-structure peaks. Note that the total number of DPOAE fine-structure peaks is different for each subject (peak frequency is represented from low, P1, to high). Error bars represent 95% confidence intervals. The left column shows the MOC reflex in dB ($MOCR_{dB}$) and the right column shows the normalized MOC reflex ($MOCR_n$).

showed less intrasubject repeatability than the reflex measured in any other frequency range, but the differences between this frequency range and others were not great. The present results suggest stability of the MOC reflex and are promising; however, they should be validated with a larger group in less-than-ideal conditions before generalizations can be made to clinical populations. It is likely that in a group with a less robust SNR (e.g., those with some mild hearing

loss or aging-related decline) or more biological noise (e.g., infants and children), the stability will be reduced.

In applying the normalized MOC metric ($MOCR_n$), one might distinguish a normally functioning auditory system from a system showing deficits if one observed a >0.05 fractional change in baseline amplitude. If we consider this as a general guideline for MOC reflex stability, the experimental variable—or, in clinical work, the treatment—would

Figure 6. Mean reflection-component medial olivocochlear reflex (MOCR_{Rn}) for each subject plotted as a function of distortion product otoacoustic emission center frequency of one-third-octave bins. Error bars represent 95% confidence intervals.

need to induce a change surpassing this natural variability in order to be detected and attributed to intervention, for example. The component-specific reflection-based MOC test was more variable and would require changes as high as 0.13 before it might be attributed to an intervention or pathology. This wider spread was most likely related to the lower reflection-component levels and associated reductions in SNR. If a reflection-type emission is to be used to gauge the MOC reflex, it may be more efficacious to use either click-evoked or stimulus frequency OAEs to maximize SNR and avoid the need for component separation, which requires signal processing and can introduce additional error into the estimates.

Comparison With Literature

Present results cannot be directly compared with previous studies that used DPOAEs without controlling for fine structure (Kumar et al., 2013; Wagner et al., 2005, 2007, 2008). Using click-evoked OAEs, de Boer and Thornton (2008) reported a mean increase in the MOC reflex of 0.63 dB on Day 4 and 0.78 dB on Day 5 when they implemented a 5-day training regimen to improve listening in adults with normal hearing. This effect exceeded the natural intrasubject variability that we reported here over 4 days (95% CIs [0.03, 0.47]) and 4 weeks (95% CIs [0.06, 0.70]), suggesting it could be appropriately attributed to the intervention regimen rather than natural day-to-day fluctuations or measurement error.

In addition to monitoring effects of therapy, carefully quantified intrasubject variability of MOC reflex may help interpret meaningful differences in the MOC reflex between normally functioning individuals and clinical populations of interest (e.g., auditory neuropathy, auditory

processing disorders, or specialized groups such as musicians). Hood et al. (2003) reported mean MOC-mediated contralateral suppression of approximately 1.5 dB overall in listeners with normal hearing. In patients diagnosed with auditory neuropathy, this value was significantly reduced by approximately 1.3 dB across both ears. With the existing intrasubject variability reported here, one might expect that these two experimental groups could be clearly distinguished. However, there are some fundamental differences between studies, which makes direct comparison problematic. Our measurement of MOC reflex was based on the DPOAE recorded at moderate levels with relatively wide f_2/f_1 ratio, indicating that the primary contributor to the ear canal DPOAE mixture was nonlinear distortion (Abdala, Dhar, & Kalluri, 2011). In contrast, Hood et al. (2003) implemented a click OAE to gauge the MOC reflex, which under a dual-source model (Shera & Guinan, 1999) is considered an emission principally produced by linear reflection and thought to be sensitive to changes in the cochlear amplifier. Our MOC test based on the reflection component of the DPOAE (MOCR_{Rn}) might correlate more closely with the data of Hood et al. (2003). If reflection-based OAEs (click-evoked OAEs, stimulus-frequency OAEs), which are theoretically more closely linked to cochlear amplifier gain and tuning, provide a more robust measure of the MOC reflex and seem to have smaller measures of intrasubject variability, as some studies suggest (Francis & Guinan, 2010; Guinan, Backus, Lilaonitkul, & Aharonson, 2003), then they may be the more useful metric for monitoring the MOC reflex.

Muchnik et al. (2004) reported that the average differences in click-evoked OAE suppression between children diagnosed with auditory processing disorder and normal-hearing controls ranged from 0.56 to 1.52 dB across all

time-window conditions/ears. This between-groups difference exceeds the intrasubject variability in the DPOAE MOC indices studied here. We might conjecture that the salient between-groups variance would exceed natural within-subject variance and allow for this important distinction. Similarly, the intrasubject variability in the DPOAE-based MOC indices reported here is less than the reported between-groups differences (approximately 0.7–1.1 dB) observed in musicians and nonmusicians (Perrot, Micheyl, Khalfa, & Collet, 1999). It must be reiterated, however, that in the absence of comparable DPOAE-based measures of the MOC reflex, we are making comparisons between OAE measures derived from different generation mechanisms.

Collectively, present results suggest that our DPOAE indices of the MOC reflex may provide (a) sufficient stability within a given subject (or patient, in clinical applications) to delineate the subtle differences in MOC reflex strength between subject groups with normal hearing and subject groups with hearing impairment and (b) possibly sufficient stability within a subject to monitor changes in the MOC reflex strength induced by treatment. However, we have not conducted a study of these DPOAE-based MOC metrics on an independent cohort to assess accuracy of diagnosis or detection (of auditory deficits) in individual ears. These hypotheses warrant further empirical study and application of these metrics to patient populations.

The normalized measures fared best. A normalization process takes into account the day-to-day fluctuations in the baseline DPOAE level that is used to compute the MOC reflex. Normalization also eliminates the effect of differences in baseline emission pressure levels on calculation of the MOC reflex. The vector-based index may provide a more comprehensive measure of the reflex because it incorporates phase changes as well as level changes and showed reliability that was comparable to the level-based estimates. Henin et al. (2011) showed that the vector analysis yielded MOC effects that were less variable among four subjects when compared with MOC reflexes measured at peaks. We did not find enhanced stability for our vector measure in this report; however, there were some differences between this study and that conducted by Henin et al. (2011). They presented an MOC elicitor at 40 dB SPL compared with our 60 dB SPL. In addition, their measures of variability were not based on repeated daily or weekly test sessions as conducted here (i.e., the definition of “variability” differed greatly from one study to the other). It may also be that the measures of stability applied here (Cronbach’s alpha and CIs) were not sufficiently sensitive to find enhanced performance for the vector difference metric. Nevertheless, MOC reflexes computed as the amplitude of the difference vector were still comparable in stability to those MOC reflex metrics normalized by DPOAE baseline amplitude.

Summary and Conclusions

Many factors were controlled in this study to maximize the stability of the MOC reflex test calculated in four different ways. The same tester conducted all tests around

the same time of day, using the same size probe tips each time. In addition, individuals with high acoustic reflex thresholds were chosen for testing to avoid this confound. We considered four different MOC reflex indices to discern whether any one was more stable than another. These four indices were chosen considering mechanisms of OAE generation and recognizing the DPOAE as a dual-mechanism response. This feature of the DPOAE was accommodated by measuring at fine-structure maxima and separating the DPOAE into a more component-specific measure, thus avoiding component interference to a large extent. This represents an ideal condition for minimizing intrasubject variability and ensuring a repeatable response. In a clinical setting with challenging patient populations, fewer variables will be under clinician control, and the SNR will be less than ideal. Until studies are conducted in realistic environments with more challenging clinical populations, the utility of this MOC reflex metric for applied purposes remains untested.

One factor that we did not control, which no doubt introduced some noise into the MOC reflex measurements, was attention. The MOC effect was evoked without any attempt to monitor or control the subject’s attention toward the contralateral noise activator. This may be relevant because the MOC effect can be modulated by attention (de Boer & Thornton, 2007; Froehlich et al., 1993; Harkrider & Bowers, 2009; Maison et al., 2001). The directions of reported attention effects are not well defined and are inconsistent; Harkrider and Bowers (2009) demonstrated decreases in the MOC reflex, whereas earlier studies showed an increase in MOC effects (Maison et al., 2001) with attention. Hence, we are not certain of the specific effects that attention might have produced in the current study; however, there is little doubt that attention varied among our subjects and within a subject during repeated testing sessions because we measured only under passive listening conditions (i.e., attention was not monitored). Controlling attention by including task-dependent measures might decrease intrasubject variability more effectively. Nevertheless, the work here suggests that DPOAE-based measures of the MOC reflex are stable over time and that natural variance from day to day or week to week is small enough to detect most of the differences described in the literature between groups with normal hearing and groups with auditory impairment and, possibly, to monitor intervention-related success. The latter is a relatively new area of research that will need to be further studied before we know the magnitude of these effects on measures of the MOC reflex. More studies are needed with larger sample sizes and with clinical populations to better understand natural versus therapeutically evoked shifts in the MOC reflex. Additionally, these MOC reflex indices should be applied to individuals with known auditory deficits to empirically assess the accuracy with which they can detect pathology.

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