Reflex Control of the Human Inner Ear: A Half-Octave Offset in Medial Efferent Feedback That Is Consistent With an Efferent Role in the Control of Masking

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1Department of Electrical Engineering and Computer Science, Massachusetts Institute of Technology, Cambridge; 2Eaton Peabody Laboratory, Massachusetts Eye and Ear Infirmary, Boston; 3Department of Otology and Laryngology, Harvard Medical School, Boston; and 4Program in Speech and Hearing Bioscience and Technology, Harvard-MIT Division of Health Sciences and Technology, Cambridge Massachusetts

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Lilaonitkul W, Guinan JJ. Reflex control of the human inner ear: A half-octave offset in medial efferent feedback that is consistent with an efferent role in the control of masking. J Neurophysiol 101: 1394–1406, 2009. First published December 31, 2008; doi:10.1152/jn.90925.2008. The high sensitivity and frequency selectivity of the mammalian cochlea is due to amplification produced by outer hair cells (OHCs) and controlled by medial olivocochlear (MOC) efferents. Data from animals led to the view that MOC fibers provide frequency-specific inhibitory feedback; however, these studies did not measure intact MOC reflexes. To test whether MOC inhibition is primarily at the frequency that elicits the MOC activity, acoustically elicited MOC effects were quantified in humans by the change in otoacoustic emissions produced by 60-dB SPL tone and half-octave-band noise elicitors at different frequencies relative to a 40-dB SPL, 1-kHz probe tone. On average, all elicitors produced MOC effects that were skewed (elicitor frequencies 1/2–1 octave below the probe produced larger effects than those 1/2–1 octave above). The largest MOC effects were from elicitors below the probe frequency for contra- and bilateral elicitors but were from elicitors centered at the probe frequency for ipsilateral elicitors. Typically, ipsilateral elicitors produced larger effects than contralateral elicitors and bilateral elicitors produced effects near the ipsi+contra sum. Elicitors at levels down to 30-dB SPL produced similar patterns. Tuning curves (TCs) interpolated from these data were V-shaped with Q10s ~ 2. These are sharper than MOC-fiber TCs found near 1 kHz in cats and guinea pigs. Because cochlear amplification is skewed (more below the best frequency of a cochlear region), these data are consistent with an anti-masking role of MOC efferents that reduces masking by reducing the cochlear amplification seen at 1 kHz.

I N T R O D U C T I O N

Descending feedback control is almost universal in sensory systems. In the cochlea, the mammalian hearing organ, feedback from the medial olivocochlear (MOC) efferent system controls the gain of “cochlear amplification,” the process responsible for the high sensitivity and frequency selectivity of mammalian hearing. Cochlear amplification is produced by electro-motile outer hair cells (OHCs) acting to amplify basilar-membrane motion in response to sound (Dallos 1992). MOC efferent fibers synapse directly on OHCs and act through cholinergic synapses with a9-α10 ACh receptors. Ca2+ enters through these receptors and activates Ca-activated K+ channels resulting in an OHC hyperpolarization that reduces OHC motility and cochlear amplification (Fuchs 2002).

MOC fibers respond to sound and are the effectors in an acoustic reflex that is commonly thought to provide frequency-specific feedback inhibition of cochlear-amplifier gain. MOC fibers have tuning curves that are only slightly wider than cochlear afferent fibers, and each MOC fiber innervates a cochlear region with a best frequency (BF) near the MOC fiber’s BF with the spread of individual fibers along the cochlea ranging from 0.1 to 1 octave (Brown 1989; Liberman and Brown 1986; Robertson 1984). From these properties, it has been suggested that there is frequency-specific MOC feedback inhibition, i.e., a sound that excites a cochlear frequency region elicits firing of MOC fibers that decreases cochlear-amplifier gain specifically in this frequency region (Winslow and Sachs 1987).

MOC feedback is thought to provide an antimasking effect that increases the discriminability of signal variations in continuous noise. MOC activity reduces masking by lowering the cochlear amplification of the response to the noise. The reduced response to the noise reduces the resulting adaptation at the IHC-to-afferent-fiber synapse and expands the response range of an auditory-nerve fiber. The auditory-nerve fiber can then respond over a wider range of firing rates to a target sound, and the resulting neural response provides better ability to discriminate small changes in the target sound (Kawase et al. 1993; Winslow and Sachs 1988). Because noise-induced effects are maximal when there is substantial noise energy in frequency regions near BF, frequency-specific feedback by the MOC reflex may provide the most effective anti-masking effect for noises that are spectrally concentrated.

At moderate sound levels, in addition to providing a feedback gain-control system to enhance dynamic range and reduce masking, MOC feedback has been suggested to provide a sensory gating system to mediate selective attention (Hernandez-Peon et al. 1956; Meric and Collet 1994) or to focus attention during learning (Veuillet et al. 2007). At high sound levels, MOC feedback reduces acoustic trauma (Maison and Liberman 2000; Rajan 1992).
MOC reflexes can be activated by sound in either ear. The resulting contralateral and ipsilateral MOC reflexes are mediated by neurons in different brain stem locations (reviewed by Guinan 1996, 2006). In humans, almost all previous studies of the MOC reflex used only contralateral sounds (for technical reasons), so how similar the ipsilateral reflex is to the contralateral reflex is largely unknown. In cats, the neurons mediating the contra- and ipsilateral reflexes produce similar effects in the cochlea when stimulated electrically (Guinan and Gifford 1988). Cat MOC-fiber responses to ipsilateral and contralateral tones are relatively similar, but their responses to ipsilateral and contralateral noise are different in several respects (Liberman 1988). Considering the preceding text, one of our objectives was to compare the effects of ipsi-, contra-, and bilateral MOC reflexes and another was to compare responses to tones and noise.

To test the hypothesis that the MOC reflexes provide frequency-specific feedback and to satisfy the other objectives, we measured MOC-reflex frequency tuning at the 1-kHz region in humans. MOC effects can be measured noninvasively in humans using otoacoustic emissions (OAEs). OAEs are sounds in the ear canal due to energy from cochlear amplification that has traveled backward through the middle ear. Thus OAEs provide an indirect monitor of the amount of cochlear amplification (Shera and Guinan 2007). In contrast to previous studies (Chéry-Croze et al. 1993; Veuillet et al. 1991), we used the most frequency-specific OAE, stimulus frequency OAEs (SFOAEs) and contra-, ipsi-, and bilateral sounds to elicit MOC activity. The results show a previously undescribed skew in MOC reflex tuning, i.e., elicitors at frequencies below the probe frequency are more effective than elicitors above the probe frequency.

METHODS

Methods overview

To measure the cochlear mechanical effects produced by sound-evoked MOC activity, we used SFOAEs. SFOAEs are low-level tones in the ear canal that are generated in healthy cochleae in response to probe tones. We interpret a sound-induced change in an SFOAE (a SFOAE) as a MOC effect because 1) electrical stimulation of MOC efferents can change otoacoustic emissions, which is consistent with the MOC-fiber synapses on OHCs acting to change the mechanical properties of the cochlea (Guinan 1990; Mountain 1980; Siegel and Kim 1982), 2) MOC fibers respond to sound (Brown 1989; Liberman and Brown 1986; Robertson 1984), and 3) acoustic stimulation produces effects on auditory-nerve responses that are similar to those produced by MOC electrical simulation, and these acoustic-stimulation effects disappear when the MOC fibers are cut (Warren and Liberman 1989a,b). For OAE changes to be interpretable as being only due to activation of MOC fibers, there must be no activation of the middle-ear-muscles (MEMs). Our test to rule out MEM effects is explained in the following text. All measurements reported here had corresponding MEM tests and showed no evidence of MEM activation. MOC effects from two ears, including MEM test results, are shown in Supplementary Fig. S1.1.

Subjects

We used data from seven subjects (4 female, 3 male; ages: 22–33 yr, average: 27.5) with normal hearing in both ears (within 20 dB re. ANSI pure tone threshold at octave frequencies 0.25–4 kHz). Subjects were rejected if they were unable to stay awake and sit still during the experiment or if they did not return to complete the study. A warning light was turned on before each stimulus presentation, and the subject was instructed to sit still while the light was on and sounds were presented. An ear was accepted only if it passed the MEM test (explained in the following text), and if the magnitude of the MOC effect elicited by a bilateral 60-dB SPL broadband noise (BBN) (100 Hz to 10 kHz) was >0 dB SPL. We screened eight subjects and rejected one; however, many of the subjects had been used in previous studies (Backus and Guinan 2006, 2007; Guinan et al. 2003) and were known to have higher-than-average MOC responses. We know of no reason why our selection of subjects with higher-than-average ΔSFOAE magnitudes would bias our results. The number of ears included for data analysis varied from 3 to 14 and, as explained in the following text, depended on the signal-to-noise ratio (SNR) and the objectives of that part of the study.

Acoustic stimuli

We used SFOAEs, instead of other OAEs, because they are the most frequency-selective OAE, and the probe sound used to evoke SFOAEs elicits relatively little MOC activity (Guinan et al. 2003). SFOAEs were simultaneously evoked in both ears by a 40-dB SPL continuous bilateral tone at a frequency within ±10% of 1 kHz, presented through one earphone of the Etymotic ER10C acoustic assembly in each ear. Although this SFOAE probe stimulus elicits less MOC activity than other OAE probe stimuli, nonetheless, it does appear to have a small effect on the results. Data that provide an estimate of this are given in RESULTS, and the implications of these data are considered in the DISCUSSION. On each subject, a probe frequency was selected that was ≥100 Hz away from any spontaneous OAE with magnitude above –10 dB SPL (This was done to avoid entrainment and other interactions) (e.g., Long et al. 1991; Zwicker and Schloth 1984) and produced the largest change in the SFOAE (ΔSFOAE) magnitude in response to a 60-dB SPL contralateral BBN. The largest ΔSFOAE was used so that the signal-to-noise ratio (SNR) criteria could be reached with the smallest number of stimulus repeats. No overall differences were found in the normalized ΔSFOAEs from frequencies selected as above versus from using 1-kHz (Backus and Guinan 2007). Measurements were conducted in a double-walled sound-attenuating room.

To elicit MOC activity, a 60-dB SPL tone or half-octave-band noise (NBN) was presented ipsi-, contra-, or bilaterally for 2.5 s. Because the probe tone was presented bilaterally, an ipsilateral elicitor for the right ear was simultaneously a contralateral elicitor for the left ear, etc. Preceding the elicitor was a 0.5-s period from which the baseline response was measured, and following the elicitor was a 2-s period for recovery, so that the resulting stimulus repetition period was 5 s. The term "elicitor frequency" will be used to refer to either the frequency of a tone elicitor or the center frequency (on a logarithmic scale) of a half-octave-band noise elicitor. Elicitors were presented at frequencies from 2.5 octaves below to 2.5 octaves above the probe frequency, in half-octave steps, and, to avoid bias, were in a randomized order. In each subject, frequency-series data gathering runs using tone or NBN elicitors were interleaved to minimize discrepancies from possible long-term variations in responses so that direct comparisons of the noise and tone results would be valid.

2 The subject number and probe frequencies were: S98, 960 Hz; S179, 900 Hz; S181, 1,100 Hz; S186, 900 Hz; S22, 980 Hz; S223, 1,000 Hz; S224, 1,000 Hz.

1 The online version of this article contains supplemental data.
The SFOAE produced by the probe tone alone, referred to as the “baseline SFOAE,” was measured by the suppression method (Guinan 1990; Kalluri and Shera 2007). With this method, a brief second tone is presented at a frequency near the probe tone and a level 20 dB, or more, above the probe tone level. This “suppressor tone” pushes OHC stereocilia into saturation regions and lowers the cochlear amplifier gain at nearby frequencies and thereby suppresses the SFOAE from the probe. Because of their different actions, we distinguish between this “two-tone suppression” and MOC “inhibition.” The baseline SFOAE was calculated from the vector difference of the ear-canal sound pressure from a 40-dB SPL probe tone, with and without a suppressor (a 60-dB SPL tone 110 Hz below the probe frequency presented for 500 ms every 1 s). Suppressor-tone runs and elicitor-frequency-series runs were interleaved. For both suppressor-tones and MOC-elicitors, 5-ms rise/fall cosine ramps were used to minimize spectral splatter. Consecutive elictor or suppressor presentations had opposite polarities so that after averaging, their acoustic waveforms would cancel and leave a residual equal to the induced change in the SFOAE. Calibration of the acoustic outputs from each of the two sound sources in each ER10C acoustic assembly were performed by presenting a spectrally-flat, random-phase, broad-band (0.1–10 kHz) electrical signal (i.e., a “noise”) to the sound source and measuring the resulting ear canal sound pressure using the microphone in the ER10C. The FFT of the microphone signal divided by the level of the electrical signal gave the calibration at each frequency. This was done at the beginning of every data gathering session and frequently within a session to account for small changes in the probe fit in the ear canal. Noise bursts were made spectrally flat at the ER10C probe tip by applying these calibrations.

Measurement analysis

Frequency-series runs were done in blocks that averaged 4–10 (always an even number) artifact-free responses at each elictor frequency. Responses were rejected as being contaminated with artifacts when the difference between one pair of responses and the next pair exceeded a criterion set for each subject. Stimulus pairs were used because elictors (or suppressors) were alternated in polarity across stimulus repetitions. Multiple data blocks were averaged to achieve averages with \( n \approx 50 \) stimulus repetitions. The averaged waveforms were then heterodyned (heterodyning is equivalent to sending the signal through a lock-in amplifier) (for more details, see Guinan et al. 2003) to obtain \( P(t) \), the magnitude and phase of the sound pressure at the probe frequency as functions of time over one repetition period [note: the magnitude and phase are expressed by the single complex time function \( P(t) \)]

\[ P(t) = \text{vector sum of the probe tone and the evoked SFOAE} \]

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To obtain MOC-effect metrics from \( \Delta \text{SFOAE}(t) \), the data were vector averaged within certain time windows. 1) A during-elicitor window: contralateral MOC elictors produced no two-tone suppression of the SFOAE, so measurements could be made during the elictor. Two during-elicitor windows were used. For contralateral data considered alone, we used a 1,000-ms time period that ended 50 ms before the end of the elictor. This long window provided the best SNR. When contralateral and ipsilateral data were in the same figure, we used a 100-ms time period (also ending 50 ms before the end of the elictor) so that all the data had comparable noise floors. 2) The post-elicitor window: ipsi- and bilateral elictors close in frequency to the probe tone produced two-tone suppression while they were on. This suppression obscured the MOC effect during the elictor. Fortunately, suppression decays in a few milliseconds, much more quickly than the decay of the MOC effect (i.e., \( t_{\text{suppression}} < 10 \text{ ms} \); \( t_{\text{MOCR}} \sim 100 \text{ ms} \) (Guinan 1990). Thus for ipsi- and bilateral elictors (and contralateral elictors when they were plotted on the same axis as the others), we used a 100-ms post-elicitor window starting 50 ms after the end of the elictor. This post-elicitor window avoids two-tone suppression but at the expense of obtaining only a decaying part of the MOC effect. 3) The noise-floor window: the noise floor was estimated by averaging \( \Delta \text{SFOAE}(t) \) over a time-window of the same length as the data-analysis-time-window (during or post-elicitor) but positioned such that the end of the noise time window was 50 ms before the end of the stimulus repetition period.

To minimize biasing effects due to noise (Backus 2007), data from each ear and elictor type were included for analysis only if the maximum \( \Delta \text{SFOAE}(t) \) from the elictor frequency series had an SNR of \( \geq 3 \) (9.5 dB). This criterion was applied to the maximum point rather than to each point individually to avoid frequency biases (i.e., to allow points to be used even if they showed no response, as long as there was a large response at some frequency in the series).

MEM contraction test

A MEM test was performed on each subject to ensure that the MEMs were not activated at the stimulus levels used. For this, a 65-dB SPL continuous suppressor tone at 110 Hz above the probe frequency was presented in addition to the normal acoustic stimuli. The rational for this test is as follows: for all evoked OAEs, the ear canal sound pressure is composed of sound from the sound source acting on the passive impedance of the middle ear at the tympanic membrane, plus the OAE originating from within the cochlea (Fig. 1). MOC efferents act only on the OAEs from within the cochlea.
whereas MEM contractions can change both the probe-source pressure (by changing the middle-ear impedance) and the OAE (by changing middle-ear transmission). However, MOC-induced changes in the SFOAE will not be detected if the SFOAE is fully suppressed, so the 65-dB SPL suppressor was added to suppress the probe-frequency SFOAE. On the other hand, even in the presence of the suppressor, MEM contractions will still affect the middle-ear impedance seen at the tympanic membrane and will produce a change in the sound pressure in the ear canal. So with this paradigm, only MEM contractions produce a change in the sound pressure at the SFOAE probe frequency. Thus with the suppressor tone on, the presence of an elicitor-induced change in the ear canal sound at the SFOAE frequency indicates there has been a MEM contraction, while responses within the noise floor are taken to mean there was no significant MEM contraction.

**Tuning curves of MOC effect**

Tuning curves of $\Delta SFOAE^n$ magnitudes (i.e., MOC effects) were obtained as equal response contours derived from elicitor frequency sweeps done at different elicitor levels. The BF was taken to be the frequency that produced the largest $\Delta SFOAE^n$ magnitude at the lowest elicitor level, and the magnitude of the $\Delta SFOAE^n$ at this BF was used as the criterion response for the equal response contour. Tuning curve (TC) points that yielded criterion $\Delta SFOAE^n$’s were calculated by interpolation of the $\Delta SFOAE^n$’s obtained at higher elicitor levels.

The TCs were derived from frequency sweeps that were repeated at 30, 45, and 60 dB SPL for NBN elicitors and 30, 45, 60, and 70 dB SPL for tone elicitors. 70-dB SPL NBN was not used because it induced MEM contractions in many subjects. Data for a particular elicitor level were included in the derivation of TCs only if the maximum $\Delta SFOAE^n$ magnitude in that frequency series had a SNR $\geq 3$ ($\sim$ 9.5 dB). All elicitor frequency series for a TC used the same 40-dB SPL probe tone (except in Fig. 6 where a 20-dB SPL probe tone was used).

**Determining the statistical significance of variations across parameters**

To determine the statistical significance of the variations of $\Delta SFOAE^n$ magnitudes obtained with variations in stimulus parameters, we employed an n-dimensional ANOVA (Matlab7.1 Statistical Toolbox) with a Bonferroni correction for multiple comparisons. These statistical tests were done only when the $\Delta SFOAE^n$ magnitudes passed the Lillifores test for normality. If they did not pass, the Friedman nonparametric two-way ANOVA was used. Statistical significance was accepted at the 0.05 level. The data were compared with the noise-window data set that measured the response under the Null-hypothesis of no $\Delta SFOAE^n$ (i.e., in the absence of an MOC-elicitor).

**Determining the statistical significance of response asymmetry**

To determine if the $\Delta SFOAE^n$ magnitudes from elicitor frequencies below the probe frequency were larger than those from above the probe frequency to a statistically significant degree, we used a bootstrap technique (Efron and Tibshirani 1993). We first determined the distribution of the skewness statistic, $b_1$, under the null hypothesis that the distribution was symmetric about the probe frequency. The skewness statistic, $b_1$ (see supplementary material) is zero for a symmetric distribution and increasingly positive (negative) for a distribution spread more to the left (right) of the mean. Under the null hypothesis of symmetry, the MOC effect is the same for elicitors the same number of octaves above or below the probe frequency. We created trial null distributions from the data actually obtained from the 11 (or 14) ears, by pooling data from above and below the probe frequency (keeping separate the data from each half-octave frequency difference from the probe frequency) and randomly choosing (with replacement) from that pool in creating each new 11 or 14 ear null distribution. From each trial Null distribution, we calculated a trial value of $b_1^{\text{null}}$. We performed 4,000 trial distributions and calculations of $b_1^{\text{null}}$ to obtain the bootstrapped distribution of $b_1^{\text{null}}$. The actual result was taken to be statistically significant if its measured $b_1^{\text{null}}$ fell outside of the 95% occurrence interval of $b_1^{\text{null}}$. This would show that the probability was <0.05 that the observed $b_1$ value could have come from the Null (symmetric) distribution.

**Results**

**Frequency tuning of contralateral-elicitor effects**

We first consider data from contralateral elicitors because they do not cause two-tone suppression in the ipsilateral (test) ear and therefore allow measurements to be made during the elicitor when the MOC effect is largest and the SNR is best. There were significant differences in the frequency patterns of the MOC effects across ears (Fig. 2, top) for both tone and noise-band elicitors (ANOVA for the probability that all MOC effects were from the same distribution showed $P_{\text{nullSame}} < 10^{-3}$, for tones and for noise bands). However, there was no significant difference between the left and right ear data (ANOVA: $P_R = L = 0.29$ for NBN, $P_R = L = 0.86$ for tones). Considering this, the right and left ear data are pooled in Fig. 2. Although the elicitor frequency that showed the largest

![Fig. 2](http://jn.physiology.org/)

**FIG. 2.** MOC effects in response to contralateral tone and half-octave-band noise (NBN) elicitors showed significant skews toward frequencies below the probe frequency. $\Delta SFOAE^n$ magnitudes as functions of elicitor frequency from 14 ears from 7 subjects. Data from a 1,000-ms during-elicitor window. Individual data are overlaid (top) and averaged (bottom). -, -, average noise floor, •-•, 2 SD above the noise floor. Significant values are marked: $\Delta = P \leq 0.05$; $\Delta\Delta = P \leq 0.01$; $\Delta\Delta\Delta = P \leq 0.001$. J Neurophysiol • VOL 101 • MARCH 2009 • www.jn.org
MOC effects varied considerably across individual ears (Fig. 2, top), this was washed out in the average across subjects (Fig. 2, bottom).

The average during-elicitor contralateral MOC effect was significantly different from the noise floor over a wide range of elicitor frequencies. Significant average MOC effects were produced by NBN elicitors from −1.5 to +1.0 octaves relative to the probe frequency (~2.5 octave span) and by tone elicitors from −1.5 to 0.5 octaves relative to the probe frequency (~1 octave span). In individual ears, there was a considerable variation in the range of the elicitor frequencies that showed significant effects. For NBN elicitors, one subject had significant MOC effects at the 0.05 level over the entire 5 octave span tested.

Figure 2 shows that the largest MOC effects were for elicitor frequencies below the probe frequency. The skew of the MOC effect (elicitors below the probe frequency more effective than elicitors above) was statistically significant for both tone and NBN elicitors (the probability that the distributions were symmetric about the probe frequency was $P_{\text{SYMMETRIC}} < 10^{-7}$ for tones; $P_{\text{SYMMETRIC}} = 7 \times 10^{-3}$ for noise). The skewness was more pronounced for tones than for noise (skewness statistic $b_1 = 0.53$ for tones and 0.23 for noise).

Frequency tuning of contra-, ipsi-, and bilateral elicitors

Measurements of MOC effects produced by ipsilateral and bilateral elicitors cannot use a during-elicitor window because the elicitor produces two-tone suppression of the SFOAE in the ear receiving the elicitor. Measurements of ipsi- and bilateral MOC effects were made using data from a post-elicitor window that captured the MOC effect after the complete decay of elicitor-induced two-tone suppression but before the MOC effect had decayed completely (see METHODS). Because MOC effects produced by contralateral elicitors can be measured in both during-elicitor and post-elicitor windows, the contralateral response provides a way of seeing how much the MOC effect is affected by measuring it in the post-elicitor window. Example data from two subjects are shown in Supplementary Fig. S1, A and C. We found no systematic differences in shape between the results from the post-elicitor versus the during-elicitor windows. However, the post-elicitor data were smaller and decayed into the noise floor at more frequencies than the during-elicitor data.

MOC effects from contralateral, ipsilateral and bilateral tone and NBN elicitors are shown for individual ears in Fig. 3 and averaged across ears in Fig. 4. All of these are from measurements in the post-elicitor window. There were large variations across subjects (ANOVA: $P_{\text{AllSame}} < 10^{-3}$ for NBN and for tones), but no statistical differences between the MOC effects in the left and right ear (from 4 subjects with statistically significant left and right ear measurements, ANOVA: $P_{R-L} = 0.61$ for NBN, $P_{R-L} = 0.56$ for tones). Thus data from the right and left ears were pooled in Figs. 3 and 4.

For ipsi- and bilateral elicitors, the range of significant average MOC effects was −1.5 to +0.5 octaves, or more, relative to the probe frequency. On individuals, the range of significant MOC effects varied across ears. For all lateralities and elicitor types, at least one ear showed significant MOC effects over the entire 5 octave range tested. In individual responses, the largest MOC effects for bi- and ipsilateral elicitors were found over a wide range of frequencies including at and above the probe frequency (Fig. 3). Again, the considerable individual differences are smoothed out in the average (Fig. 4). In general, the SNR of the data from most of the individual ears is good enough to say that the differences across ears are not artifacts of measurement noise (e.g., note the small error bars in the data of Suppplementary Fig. S1).

In general, the average MOC effect at each frequency was greater for bilateral elicitors than either ipsi- or contralateral elicitors, and, to a first order, the bilateral effect approximately equaled the sum of the ipsi and contra effects. At many elicitor frequencies, the MOC effect was greater for ipsilateral elicitors than for contralateral elicitors, with the biggest difference being when the elicitor was near the probe frequency.

For all three lateralities, elicitor frequencies lower than the probe frequency produced larger MOC effects, on average, than elicitor frequencies above the probe frequency (Fig. 4). The skewness was significant at the $P < 0.05$ level for all three lateralities. In addition, the skewness was more pronounced in responses to tones than to NBN ($b_{1-TONE} > b_{1-NBN}$) consistently across all lateralities. The skewness factors and hypothesis test results are in Supplementary Table S1. Although

![Graph of MOC effects versus elicitor-frequency data](http://jn.physiology.org/)

FIG. 3. Variation of MOC-effect versus elicitor-frequency data across individual ears for contra-, ipsi- and bilateral elicitors. Shown are the ∆SFOAE magnitudes versus elicitor frequency for 60-dB SPL elicitors for the 11 ears from 7 subjects that met the SNR criteria. All data are from the post-elicitor window.
ipsilateral elicitors showed significant skew, the largest average MOC effects were from ipsilateral elicitors centered at the probe frequency. For contra- and bilateral elicitors, the largest average MOC effects were for elicitors below the probe frequency.

MOC frequency tuning for elicitors at multiple sound levels and MOC-effect TCs

Although the data in Figs. 2–4 show that MOC effects from 60-dB SPL elicitors are skewed toward lower frequencies being more effective, it seemed possible that elicitors at lower sound levels (where sounds need to be closer to the probe frequency to produce masking than they do at 60 dB SPL) might show frequency tuning more centered on the probe frequency. To test this hypothesis, we gathered data with elicitors at sound levels from 30 to 70 dB SPL. Because the data for a single-laterality frequency-response plot took at least five subject hours to obtain, we obtained these extensive sets of data only for six ears (3 subjects).

The data on MOC effects from elicitors at different sound levels allowed us to calculate TCs, plots of the stimulus necessary to achieve a criterion response. Such equal-response contours have the advantage of minimizing the effects of nonlinearities in the stages leading up to the response, and they provide a convenient way to summarize data from many elicitor levels. Because TCs for tone stimuli are most common throughout the literature, we emphasized obtaining TCs from tone elicitors rather than from NBN elicitors.

First, we consider data from contralateral elicitors because, as noted earlier, MOC effects from contralateral elicitors can be measured during the elicitor presentation and have the best SNR. In addition we can measure contralateral effects in both during and post-elicitor windows which allows these results to be compared. As the level of the contralateral elicitor tone was changed, the shape of the MOC-effect versus elicitor-frequency function changed somewhat, but the frequency that produced the maximum MOC effect remained the same, i.e., at a frequency below the probe frequency (Fig. 5). Thus the tip frequency of the resulting TCs (the frequency with the highest response at the lowest elicitor level) was below the probe frequency. The TCs derived by interpolation from the MOC effects of the various contralateral elicitor levels and frequencies are shown in Fig. 5, bottom. The TCs had tip frequencies one-half octave below the probe and relatively narrow V-shaped tips that widened considerably at high levels. The TCs from during-elicitor versus post-elicitor windows were similar but not identical (Fig. 5, bottom).

The sharpness of tuning for auditory-nerve fibers and MOC neurons is conventionally quantified by a dimensionless measure, Q10, the bandwidth/BF ratio where BF is the best frequency (the tip frequency in the present context) and the frequency function changed somewhat, but the frequency that produced the maximum MOC effect remained the same, i.e., at a frequency below the probe frequency (Fig. 5). Thus the tip frequency of the resulting TCs (the frequency with the highest response at the lowest elicitor level) was below the probe frequency. The TCs derived by interpolation from the MOC effects of the various contralateral elicitor levels and frequencies are shown in Fig. 5, bottom. The TCs had tip frequencies one-half octave below the probe and relatively narrow V-shaped tips that widened considerably at high levels. The TCs from during-elicitor versus post-elicitor windows were similar but not identical (Fig. 5, bottom).

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TC bandwidth is measured at a level 10 dB above the “threshold” at the BF. The Q10s from contralateral-elicitor-tone TCs averaged 2 (range: 1.3–3.3; values in Supplementary Table S2).

TCs from ipsi- and bilateral elicitors were calculated from post-elicitor window data. In these TCs, the tip frequency was always displaced from the probe frequency and the TCs became very wide at high levels (Supplementary Fig. S2), which is similar to the contralateral TCs of Fig. 5. Most of the tone TCs had tip frequencies that were 0.5 or 1 octave below the probe frequency; however, one was above the probe frequency. The mean Q10 values for contra-, ipsi-, and bilateral tone elicitors were all near 2 (Supplementary Table S2).

In two subjects, TCs were obtained with NBN elicitors. The NBN-elicitor TCs were always wider than the tone-elicitor TCs (Supplementary Table S3) and more often had tip frequencies above the probe frequency (Supplementary Fig. S3). These TC properties are consistent with the previous finding that NBN elicitors produce MOC effects over a wider range of elicitor frequencies than tones and are more effective than tones for elicitor frequencies above the probe frequency (Figs. 2–4).

Overall, the MOC-effect frequency functions for elicitor levels below 60 dB SPL do not support the hypothesis that the MOC effect becomes centered at the probe frequency as the elicitor level is lowered.

Frequency specificity measured with 20 versus 40-dB SPL probe tones

To see if using a 40-dB SPL probe tone influenced the results, in one subject elicitor-frequency series at four elicitor levels were repeated using a 20-dB SPL probe tone. Figure 6 shows the MOC effects from both 20- and 40-dB SPL probes as well as the TCs derived from them. The 20-dB SPL data had poorer SNRs than the 40-dB SPL data, and this exerted a considerable influence on the results. For instance, with the 20-dB SPL probe, the contralateral MOC effects from the post-elicitor window did not pass the SNR criteria (see Methods) so Fig. 6 shows only during-elicitor contralateral data.

One notable feature of the results is that the MOC effects from the 20-dB SPL probes generally are larger than those from the 40-dB SPL probes. For the ipsilateral highest-level elicitors, the MOC effects were more than twice as large (Fig. 6: B vs. E). However, for the 20-dB SPL probes and low-level elicitors, the MOC effects appeared to be relatively lower, as if the threshold for eliciting an MOC effect was higher with the

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**Fig. 6.** Measurements of MOC effects with probes at 20 and 40 dB SPL show some differences in shape indicating that probe level may affect the results. A–F: ∆SFOAE magnitude versus elicitor frequency for tone elicitors at 4 levels and two probe intensities. The bi- and ipsilateral data were from the post-elicitor window. The contralateral data were from a during-elicitor window. G–I: the TCs derived from the data at top. Error bars in A–F are 1 SE. Q10 values in Supplementary Table S4. Subject 181R.
20-dB SPL probe. In many places, it is difficult to be sure this is happening because of poor SNRs, but for bilateral tone elicitors at frequencies below the probe frequency, an increase in elicitor threshold seems clear (Fig. 6: A vs. D).

The low SNRs make the TCs from the 20-dB SPL probes difficult to compare in detail to the TCs from the 40-dB SPL probes. For the 20-dB SPL probes, the lowest-level contra- and ipsilateral elicitor-frequency series did not pass the SNR criterion, so the TCs derived from these have tips at the next highest level, 45 dB SPL. The Q10s from the 20-dB SPL probes were wider than those from the 40-dB SPL probes (Supplementary Table S4), but this difference is at least partly due to the higher tip level. For high-level elicitors, the TCs from the 20-dB SPL probes appear to be narrower than those from the 40-dB SPL probes, but again this may be due to using the 45-dB SPL elicitor data to get the TC tip frequency that sets a higher criterion for the rest of the TC. One interesting feature in the bilateral data is the shift of the TC tip frequency from below to above the probe frequency (Fig. 6G). This appears to be due to the large decrease in elicitor threshold for elicitor frequencies below the probe frequency in the bilateral data (Fig. 6, left). It should be pointed out that the 20-dB SPL data were all obtained after the 40-dB SPL data and this subject showed SOAE variability so some of the difference between the 20- and 40-dB results may be due to subject variability over time. The implications of these data will be considered in the discussion.

Frequency specificity measured with uni- versus bilateral probe tones

To ascertain the extent to which our use of bilateral (instead of unilateral) probe tones may have affected the results, we did tests on two subjects. The tests were designed to determine if the skew in the elicitor frequency response was somehow due to the use of bilateral probe tones. For this, we selected two of the original subjects who had skewed frequency patterns (finding no change in subjects with symmetric response patterns would not test the hypothesis). We also used only contralateral elicitors because these show the most skewed response patterns and are the easiest to test (responses could be measured in during-elicitor windows). Tests were run in multiple (4–9) interleaved blocks of bilateral versus unilateral 40-dB SPL probe tones, each averaging eight 5-s waveforms at 11 frequencies of 60-dB SPL half-octave noise band elicitors. The resulting data show relatively small differences between the responses with bi- versus unilateral probe tones (Fig. 7). The most obvious difference is a lower peak with unilateral compared with bilateral probes for elicitors at 1.5 octaves below the probe frequency in subject 222, but this is offset by a reduced response for elicitor frequencies above the probe so that the overall skew hardly changed (bilateral: 1.02, unilateral: 0.98). Subject 98 shows less dramatic, but similar changes and, again, the overall skew hardly changed (bilateral: 0.79, unilateral: 0.80). When looked at as the increase in the response when using bilateral probes compared with unilateral probes (Fig. 7, C and D), the pattern in the two cases is remarkably similar. However, because there are only two cases, the generality of the pattern cannot be considered reliable. Perhaps more reliable is the fact that bilateral probes typically produced larger responses than unilateral probes. In any event, the data show that the skew of the response was changed very little by the use of bi- versus unilateral probe tones.

Also shown in Fig. 7 are the original data from these two subjects (who happen to be the subjects with the largest and smallest response peaks in Fig. 2). The new data from bilateral probe tones shows some change in overall amplitudes but little change in the shapes of the responses even though the new data were obtained over 21 mo (subject 98) and 20 mo (subject 222) after the original data.

DISCUSSION

Summary of principal findings

MOC-effect frequency functions showed considerable heterogeneity across ears, but several patterns were found in the averages across ears. For 60-dB SPL contra-, ipsi-, and bilateral elicitors, the average MOC effect as a function of elicitor frequency was skewed such that elicitor frequencies below the probe frequency produced larger effects than elicitor frequencies above the probe frequency. For contra- and bilateral elicitors, the largest average MOC effects were for elicitors centered at the probe frequency. On average, ipsilateral elicitors produced larger effects than contralateral elicitors, and bilateral elicitors produced effects near the ipsi+contra sum. On average, tone elicitors produced MOC effects that were more focused and skewed in frequency than half-octave-noise elicitors.

For elicitors at levels <60 dB SPL, MOC effects as functions of elicitor frequency remained skewed, and none had a most effective elicitor frequency at the probe frequency. TCs from tone elicitors had V-shaped tips with Q10 values near 2 and tip frequencies that were displaced from (usually below) the probe frequency. TCs from half-octave-noise elicitors were wider than TCs from tones and had more variation in their tip frequencies.
Methodological considerations

Before considering what function might be served by the skew in the MOC tuning pattern, we first need to consider the adequacy of our methods. From the data of Fig. 6, it appears that the 40-dB SPL probe tone has influenced the results. The increase in MOC effect for the 20- versus the 40-dB SPL probe is expected, considering that MOC inhibition of cochlear amplification has larger effects at lower probe levels (reviewed by Guinan 1996). More relevant here, the pattern of MOC effects versus elicitor frequency appears to be different for 20- versus 40-dB SPL probes, at least for the low-level elicitors. The observed change is consistent with the hypothesis that the 40-dB SPL probe tone facilitated the MOC effect thereby lowering its threshold, more for elicitor frequencies below, than above, the probe frequency. An alternate hypothesis is that the ear changed over time. Whichever is correct, these data point out that even for the 40-dB SPL tone, which by itself elicits relatively little MOC activity (Guinan et al. 2003), the probe sound may influence the results.

Our data comparing uni- versus bilateral probe tones showed that the results did change to some extent depending on which probe was used, but, importantly, there was almost no change in the skewness of the responses. Comparing uni- versus bilateral elicitors, the binaural response was approximately the sum of the responses to the ipsi- and contralateral elicitors; this suggests that for these stimuli, there was no large systematic overall facilitation for bi- versus unilateral elicitors. Thus for both probe tones and elicitors, having the sound be bi- versus unilateral does not appear to produce fundamental changes in the patterns of the resulting MOC effects.

Overall, it must be acknowledged that the use of a 40-dB SPL bilateral probe tone might have systematically influenced our results. An important question to consider is whether the presence of our 40-dB SPL bilateral probe is what caused the 60-dB SPL elicitors to show the greatest effect ½ to 1 octave below the probe frequency instead of at the probe frequency. We cannot rule this out, but the data of Fig. 7 argue against this interpretation. Furthermore, such an interpretation assumes that only when there is no probe sound is the MOC effect centered at the cochlear frequency region that is most affected, and that the presence of a 40-dB SPL probe in this frequency region moves the most-effective 60-dB SPL elicitor ½-1 octave lower. Note that with a contralateral elicitor and no probe sound, there is no ipsilateral elicitor to inhibit so the frequency pattern of the MOC effect is moot. All measurements of MOC effects in humans using OAEs must present a probe stimulus to evoke the OAE, and this probe stimulus may have an effect on the results. Our 40-dB SPL probe is the weakest elicitor of MOC effects of any OAE probe stimulus (Guinan et al. 2003). Although we used a 20-dB SPL probe tone in Fig. 5, such a low-level probe is impractical to use in all but the best ears. Thus the 40-dB SPL probe is close to the best that can be done even though the use of such probes leaves a degree of uncertainty of how much the probe influenced the results.

What function might be served by having elicitors below the probe frequency be most effective?

To understand why MOC effects are skewed so that elicitor frequencies below the probe frequency are more effective than those above, we must first understand normal MOC function. At the moderate sound levels of our experiments, the primary function of the MOC acoustic reflex is thought to be to adjust cochlear amplifier gain to reduce the masking of rapid changes in a target sound produced by low-level background noise, both broadband and narrow-band noises (see review by Guinan 2006). Masking by a low-level ongoing noise is produced by narrowing the available range of firing rates over which auditory-nerve (AN) fibers can respond to target sound fluctuations. The AN rate range is narrowed because the background rate is increased by the noise, and the maximum rate is lowered by adaptation at the IHC-auditory-nerve synapse caused by the noise. MOC activity expands the available AN rate range both by lowering the response to the ongoing noise and by reducing the adaptation caused by the noise. The response to a target sound can cause additional adaptation and can elicit additional MOC activity, but both of these take many tens of milliseconds to fully develop, so the transient onset response to the target sound is what receives the most antimasking benefit from the ongoing MOC activity. The larger available AN-rate range increases the discriminability of target sound fluctuations, i.e., the ability of a listener to discern small changes in the target sound (e.g., because an increase of 1 dB in the sound will evoke more spikes with the increased AN-rate range). In contrast, ongoing MOC activity does not improve a target sound’s threshold because the advantage of having reduced the noise response is nearly balanced out by the MOC inhibitory effect on the response to the target sound (Kawase et al. 1993).

A variety of experiments in humans have sought to test this model of MOC function with mixed results (e.g., Giraud et al. 1997; Michely et al. 1997; Kuman and Vanaja 2004; Scharf et al. 1997; Wagner et al. 2008; Zeng et al. 1994). The most common kind of experiment has attempted to correlate the strength of the MOC reflex with the ability to detect or discriminate a target signal in noise. These studies presume that if the hypothesis is true, then individuals with stronger MOC reflexes will be better able to discriminate target signals in noise. Veuillet et al. (2007; also see de Boer and Thornton 2008) found that the correlation of MOC strength with psychophysical performance changed due to training, so it may matter whether MOC strength is measured before or after psychophysical performance is measured. Typically MOC strength has been measured by activating the reflex with contralateral noise and measuring the change in an otoacoustic emission in the ipsilateral ear, the ear that is used for the detection of the signal in noise. With this and similar paradigms, some studies found that the ability to detect changes in signals in noise was positively correlated with MOC strength, whereas other studies found no correlation. In many cases, the lack of correlation seems attributable to using a psychophysical test that is more like a threshold test than a discrimination task, using constant target signals with onsets and offsets identical to the noise duration, and/or using an inadequate SNR of the OAE. Because the MOC effect is determined by the difference between two measurements, a much higher SNR is needed when measuring MOC strength than for simply measuring the amplitude of the OAE.5 Thus while the results of these tests

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5 Note that our 9 dB SNR criterion is not for the SFOAE SNR but was applied after the subtraction of the two SFOAE measurements, which is where the SNR criterion should be applied in all studies of MOC effects on OAEs.
have been mixed, an overall assessment of the results supports the hypothesis that MOC efferents serve an antimasking role in humans by lowering cochlear-amplifier gain.

With this background we can now consider what benefit might come from elicitor frequencies below the 1-kHz probe frequency producing greater MOC effects than elicitors above the probe frequency. The MOC-induced increase in signal discriminability comes from the MOC reduction in cochlear amplifier gain reducing the response to the background noise and expanding the response range of AN fibers (Kawase et al. 1993; Winslow and Sachs 1988). The frequency tuning of the gain change needed for this has received little attention in the literature. Because broad-band noise is a far more potent elicitor of MOC activity than narrow-band noise (Lisowska et al. 2002; Maison et al. 2000; Micheyl et al. 1999; Norman and Thornton 1993; Velenovsky and Glattke 2002), most attention has been given to the effects of BBN on masking and for this circumstance MOC reflex tuning has no relevance. Nonetheless, maskers with restricted bandwidths do occur, and a possible reason that MOC feedback is skewed is to provide anti-masking under these circumstances. For expanding the response range of an AN fiber, the only gain reduction that counts is in the gain seen by that AN fiber, i.e., the gain at its CF place. Noise components outside of the amplified frequency region may produce responses and IHC adaptation that narrows that fiber’s available rate range, but changing cochlear amplifier gain will not change this. Thus for increasing the discriminability of signal fluctuations in continuous noise, MOC feedback should have tuning similar to that of the cochlear amplifier as seen by the AN fiber affected.

The frequency range over which sounds receive cochlear amplification as seen at the 1-kHz cochlear place in humans is unknown, but an estimate is provided by the gain functions derived from Wiener-kernel measurements in chinchillas (Shera 2007). For frequency regions less than ~2 kHz, these functions show positive gain from the frequency of the local BF to about one octave lower in frequency. Thus to increase the discriminability of a target 1-kHz signal in continuous noise, MOC feedback should decrease cochlear amplifier gain from ~1 kHz to 500 Hz as seen at the 1-kHz place. This corresponds fairly well to the region that produces the greatest MOC effect (Figs. 2–4). This correspondence is consistent with the hypothesis that at moderate sound levels, one role of MOC efferents is to reduce cochlear amplifier gain so as to decrease the narrowing of the available AN rate range caused by low-level, amplified continuous sounds, thereby enabling better discrimination of signal fluctuations in ongoing noise.

The correspondence between the MOC effects we have found and the expected cochlear-amplifier gain, while similar overall, is not exact, which may indicate that other factors are also important. For instance, with the preceding reasoning, one would expect MOC effects to decrease rapidly as elicitor frequency is increased above the probe frequency, but this is not the pattern that was observed. Many factors might lead to the spread of the MOC effect across frequency including spread in MOC innervation patterns and effects of the afferent Type II neural network that interconnects OHCs by reciprocal synapses (Thiers et al. 2002a,b, 2008). Somewhat more surprising is the pattern in some subjects in which there are large MOC effects above and below the probe frequency and much less at the probe frequency (e.g., as in Fig. 6, A and D). The origin and/or usefulness of this pattern is unknown.

Comparison with previous results

In humans, Veuillet et al. (1991) and Chéry-Croze et al. (1993) used contralateral 1/3-octave bands of noise swept in frequency and measured changes in transient-evoked otoacoustic emissions (TEOAEs) and distortion product otoacoustic emissions (DPOAEs), respectively. Both studies concluded that the largest MOC effects were for elicitor frequency bands near the probe frequency, although both show cases where the most effective elicitor frequency was ~1/2 octave below the probe frequency. Results similar to ours were found by Warren and Liberman (1988b) in cat auditory-nerve fibers. For fibers with BFs near 2 kHz that were excited by an ipsilateral low-level BF tone, contralateral elicitor tones produced the greatest MOC inhibitions when they were ~1/2-1 octave below the fiber BF (using cat 2-kHz fibers may be equivalent to probing the 1-kHz region in humans). The origin of the difference in results between the mostly-probe-centered patterns of Veuillet et al. (1991) and Chéry-Croze et al. (1993), and the skewed-to-lower-frequency patterns found here and by Warren and Liberman (1988b) is unclear. Both the present paper and Warren and Liberman (1988b) used tones as the probe stimulus. Tones provide the most frequency-specific measurement, and low-level tones evoke less MOC activity than the probe stimuli used in the other studies. Veuillet et al. (1991) used 50/s tone pips as a probe stimulus, a potent elicitor of MOC activity (Guinan et al. 2003). It seems possible that Veuillet et al.’s probe facilitated eliciting MOC activity when the contralateral elicitor was similar in frequency to the ipsilateral probe (whereas our 40-dB SPL probe is not immune to this, it is a far less potent elicitor of MOC activity and would be expected to influence the measurement less than Veuillet et al.’s probe). Chéry-Croze et al. (1993) used two-tone probe stimuli, which elicit more MOC activity than single tones, but <50/s tone pips, so the probe would be expected to have an intermediate level of influence on the results. However, the complexity and lower frequency specificity of DPOAEs are probably more important in producing the difference between their results and ours.

Another consideration is that the relationship between MOC effects on OAEs and the corresponding, functionally important inhibition of auditory-nerve fibers is not known for any OAE. In cats, the effect of contralateral sound on DPOAEs was not a good index of neural inhibition (Puria et al. 1996), although the results of Maison and Liberman (2000) indicate that there is some degree of correspondence between DPOAE inhibition and functional effects. On the other hand, as described in the preceding text, the pattern of effects of contralateral sound on human SFPOAEs is similar to that on cat auditory-nerve fibers, which supports our measure of MOC effect, ΔSFPOAE, as being a good index of neural inhibition. However, more data are needed before this question can be considered as settled.

All of the preceding studies indicate that the tuning of the MOC reflex is broad for moderate-level contralateral sounds. All four studies show MOC effects the amplitudes of which were greater than half of the peak MOC effect for elicitors spread over at least two octaves. Maison et al. (2000) provides concuring evidence: with elicitor SPL kept constant, MOC
effects on OAEs increased with contralateral noise bandwidth up to at least two octaves. Thus all of these studies indicate that for cochlear frequency regions near 1–2 kHz, substantial MOC effects are produced by moderate-level contralateral sounds spanning 2 octaves, or more, around the probe frequency.

Our results provide the first report of MOC-effect TCs in humans. Near 1 kHz, human MOC-effect TCs (Q10’s ~2) are sharper than cat and guinea pig MOC-fiber TCs (Q10’s 1–1.5) (Brown 1989; Liberman and Brown 1986). The sharper efferent Q10’s for humans than for experimental animals may parallel a sharper overall cochlear tuning in humans than in animals (Shera et al. 2002).

The greater effectiveness of elicitors below, rather than above, the probe frequency implies that MOC fibers that innervate the 1-kHz cochlear-amplifier region have BFs that are mostly lower than 1 kHz (i.e., these MOC fibers innervate a cochlear region more basal than their BF). In contrast, in guinea pigs, MOC-fiber BFs were generally higher than the BF of the cochlear region they innervated (Brown 2002). The origin of this difference is unknown.

**Effects of elicitor laterality and tone versus noise elicitors**

All elicitor classes produced MOC effects that were skewed, but the skew was more prominent in tone than noise elicitors and in contralateral compared with ipsilateral elicitors (Fig. 4). The most dramatic difference was for tone elicitors at the probe frequency where an ipsilateral tone elicited a large MOC effect, whereas a contralateral tone elicited an MOC effect that was barely above the noise (Fig. 4A). Tones have been reported as being ineffective elicitors of MOC activity (e.g., Berlin et al. 1993; Lisowska et al. 2002), but these studies only used contralateral tones, and ipsilateral tones appear to be much more effective. In contrast, 60-dB SPL broad-band noise, whether ipsi-, contra-, or bilateral noise, is far more effective than tones. We found that MOC effects from bilateral reflexes were often nearly the sum of the effects from the ipsi- and contralateral reflexes. This indicates that, on average, there was little binaural facilitation (or occlusion). However, some stimulus combinations may produce binaural facilitation (e.g., Fig. 6), whereas others do not. Although the ipsi- and contralateral MOC reflexes primarily involve neurons on opposite sides of the brain stem (see reviews by Guinan 1996, 2006), the data of Fig. 4 show that these reflexes are similar in some respects and different in others. Thus studies of the MOC reflexes need to measure both reflexes to get the full picture of what these reflexes do.

The generally greater effects that are produced by ipsilateral compared with contralateral elicitors may be due to there being more MOC fibers that respond to ipsilateral sound than to contralateral sound. Animal studies have reported that approximately twice as many MOC neurons respond to ipsilateral sound than to contralateral sound and correspondingly, there are twice as many crossed MOC fibers than uncrossed MOC fibers\(^6\) (reviewed by Guinan 1996, 2006). Although our data are consistent with the hypothesis that humans also have more crossed ipsilateral-reflex MOC fibers than uncrossed contralateral-reflex MOC fibers, the data are more complicated. The ratio of ipsi/contra effects depends on the frequency of the elicitor, particularly for tone elicitors (Fig. 4). This indicates that the MOC activation pattern in the brain stem varies with elicitor frequency and is not simply indicative of the ipsi/contra innervation ratio in the cochlea. The difference between the tone and NBN elicitor frequency patterns is also consistent with brain stem neurons playing a role in producing the MOC-reflex activation patterns. It may be that these different MOC activation patterns have evolved to deal with common patterns of sounds that are heard, but more evidence is needed on this issue.

**Other implications of the results for the role of MOC efferents in hearing**

Efferent effects on psychophysical tuning curves (pTCs) measured in humans show different effects above versus below the probe frequency (Kawase et al. 2000; Vinay and Moore 2008), and this pattern may be related to the skew in the effectiveness of MOC elicitors. MOC activity that affects the probe frequency is elicited both by the contralateral noise (which was intended to elicit MOC activity) and by the masking tone. Our results show that masking tones below the probe frequency evoke more MOC effect at the probe frequency than masking tone above the probe frequency. In addition, the responses of both the probe tone and the masker tone are inhibited by the MOC activity elicited by the contralateral noise. How all of these factors shape the results is difficult to interpret. However, it seems reasonable to think that the asymmetry seen in efferent effects on pTCs and the skew in our results are related.

Many published auditory experiments need to be re-examined in light of our results showing that MOC effects extend over a wider and different frequency range than previously appreciated. For instance, many studies measured responses at a test frequency with and without tones below this frequency and made the assumption (now rendered questionable) that there are no MOC effects involved (e.g., Nelson et al. 2001; Oxenham and Plack 1998; see Johnson et al. 2008 for a review). In other experiments, notched noise stimuli have been used to prevent “off-frequency listening” (e.g., Glassberg and Moore 1990), but effects of MOC activity elicited by this noise were ignored. “Overshoot,” the phenomenon that a brief signal masked by simultaneous noise shows greater masking when the signal is near the onset of a masker than when the signal is delayed >100 ms after the start of the masker, has long been thought to have efferent involvement. However, overshoot is greatest for maskers above the probe frequency (Schmidt and Zwicker 1991; Zwicker 1965), whereas MOC effects are greatest for elicitors below the probe frequency. Overshoot needs a reexamination in light of this new knowledge. There have been animal experiments directed at determining whether MOC efferents aid discrimination of target signals in background noise (e.g., May and McQuone 1995; May et al. 2004), but these did not have the benefit of knowing that the optimum noise stimulus may be a noise band centered at a frequency below the probe frequency. Auditory system models intended to gain understanding of auditory function, or as parts of speech recognition systems, often include feedback intended to mimic the effects of medial efferents (e.g., Ferry and Meddis 2007; Ghitza et al. 2007). Our data now show that, at least for frequencies near 1 kHz, to accurately mimic the human audi-
torical system, these models should use a feedback frequency pattern with a skew toward elicitors below the probe frequency being more effective than those above, the pattern we have found here.

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