Frequency Specificity of Contralateral, Ipsilateral and Bilateral Medial Olivocochlear Acoustic Reflexes in Humans

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Abstract

A variety of evidence indicates that the brain controls the gain of mechanical amplification in the cochlea in a frequency specific manner through the medial olivocochlear (MOC) efferent pathway, but the degree of MOC frequency specificity in humans is poorly understood. This thesis investigates the tuning properties of the human MOC acoustic reflex at different cochlear frequency regions and with different MOC-elicitor lateralities and frequency contents. Effects produced by the MOC reflex were quantified by the magnitude of the induced changes in stimulus frequency otoacoustic emissions (deltaSFOAEs) at probe frequencies of 0.5, 1 and 4 kHz. With MOC activity elicited by a mid-level (60 dB SPL) tone or half-octave-band of noise, significant MOC-induced deltaSFOAEs were seen over a wide range of elicitor frequencies, e.g. for elicitor frequencies at least 1½ octaves away from each probe frequency. deltaSFOAE-versus-elicitor-frequency patterns were sometimes skewed so that elicitors at frequencies above (0.5 kHz probe) or below (1 kHz probe) the probe frequency were most effective. In contrast to the wide frequency range of MOC effects from mid-level elicitors, for 1 kHz probes MOC-effect tuning curves (TCs) were narrow with Q10s of ~2, sharper than the MOC-fiber TCs with best frequencies near 1 kHz in cats and guinea pigs. When MOC effects were looked at as the MOC-inhibited SFOAE relative to the original SFOAE, the SFOAE magnitude decreases and phase changes appeared to be separate functions of elicitor frequency: SFOAE magnitude inhibition was largest for on-frequency elicitors (elicitor frequencies near the probe frequency) while MOC-induced SFOAE phase leads were largest for off-frequency elicitors. One hypothesis to account for this is that on-frequency elicitors predominantly inhibit the traveling wave from the probe-tone, whereas off-frequency elicitors shift it along the frequency axis by selectively inhibiting apical or basal parts of the traveling-wave. These results are consistent with an anti-masking role of MOC efferents and suggest that MOC efferents do more than just provide feedback to a narrow frequency region around the elicitor frequency.

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Chapter 1: Thesis Introduction and Outline

I. Introduction

A variety of evidence indicates that the brain controls the gain of the cochlea in a frequency specific manner through the medial olivocochlear (MOC) efferent pathway, but the degree of MOC frequency specificity in humans is poorly understood. Moreover, the role that medial efferents play in hearing is unclear although there have been several theories based on known anatomical and physiological evidence: gain control and dynamic range adjustment, selective attention in hearing, protection against very loud sounds and finally, enhancement of detection of brief signals in background noise. This thesis aims to investigate the MOC acoustic reflex's tuning properties for different cochlear frequency regions and with different MOC elicitor lateralities. Knowing the reflex tuning properties should give insight into, and put constraints on, the role of MOC efferents in hearing.

To study the effect of probe and elicitor frequency on the ipsilateral, contralateral and bilateral medial efferent responses in humans, efferent activation was evoked by tones or bands of noise with different spectral content, and the resulting changes in ear-canal sound pressure were recorded. The metric for MOC effect was the MOC-induced change in stimulus frequency otoacoustic emissions (SFOAEs) from 40 dB SPL probe tones near 0.5, 1, and 4 kHz.

The results in chapter 2 show that MOC-effect tuning curves (TCs) at 1 kHz were sharper than MOC-fiber TCs at 1 kHz in animals. The frequency specificity of MOC effects in response to mid-level (60 dB SPL) elicitors varied as a function of elicitor frequency, laterality and bandwidth but was surprisingly wide and exhibited a skew towards elicitor frequencies being most effective when they were below the probe frequency. This is not consistent with conventional theories of gain control in audition. Results in chapter 3 showed that MOC effects as a function of elicitor frequency were different for probe frequencies near 0.5, 1 or 4 kHz. This chapter also showed that the MOC effects could reduce the magnitude of the SFOAE and/or introduce a phase lead in the SFOAE and that these two effects need not occur together. This suggests that MOC effects on SFOAEs are more complicated than a simple reduction in the basilar membrane mechanical response to the probe frequency. Chapter 4 revealed that the MOC reflex amplitude increased with increasing elicitor bandwidth up to bandwidths of 4 octaves or more. In terms of functional organization, the relative Ipsi/Contra reflex strength (Chapter 5) varied systematically for all probe frequency regions such that the ratio was greatest when efferent activity was elicited from cochlear regions close to the probe frequency. This suggests that the relative ipsilateral and contralateral reflex "strengths" are controlled primarily by central nervous system processing rather than being determined by a fixed relative innervation density along the cochlea. In chapter 6, the data revealed that bilateral summation can occur at probe frequencies of 1 and 4 kHz when MOC activity was elicited with wide bands of noise. In contrast, with tones or narrowband noises, the bilateral MOC effects were well approximated by the complex sum of the ipsilateral and contralateral effects.

On the whole, findings are consistent with the hypothesis that efferents may improve signal detection in background noise. However, the data also suggests that efferent effects induced by efferents near the probe frequency may affect cochlear mechanics differently for effects induced by on-frequency versus off-frequency elicitors. Our results raise important questions on theories of auditory gain control.

II. Background

The olivocochlear (OC) neurons form a feedback control system that relays centrally processed sound information back to the cochlea to control the gain of cochlear mechanical response (Guinan, 1996). There are two distinct groups of OC neurons, namely the medial olivocochlear (MOC) and the Lateral olivocochlear neurons (LOC). MOC neurons originate in the medial part of the superior olivary complex and project to outer hair-cells (OHC) in the periphery, while LOC neurons originate in a more lateral region of the olivary complex and project onto dendrites of afferent neurons near inner hair-cells (IHC). LOC excitation can result in an increase or decrease in activity of the cochlea's primary afferents, the type-I auditory nerve fibers, with a time constant on the order of minutes (Groff and Liberman, 2003). LOC efferents may help balance interaural neural excitability as required for accurate localization of sounds in space (Darrow et. al., 2006). But LOC efferents have no known effects on the biomechanics of the cochlea. MOC efferent responses, on the other hand, can alter the sensitivity of cochlear responses (Galambos et al., 1956), affect cochlear mechanics (Mountain, 1980; Siegel and Kim, 1982) and affect auditory nerve fiber response to sounds (Wiederhold and Kiang, 1970). MOC efferents are reported to operate on shorter time scales than LOC efferents with 'fast effects' on the order of tens of ms and 'slow effects' on the order of tens of seconds (Cooper and Guinan, 2006, Backus and Guinan, 2007).

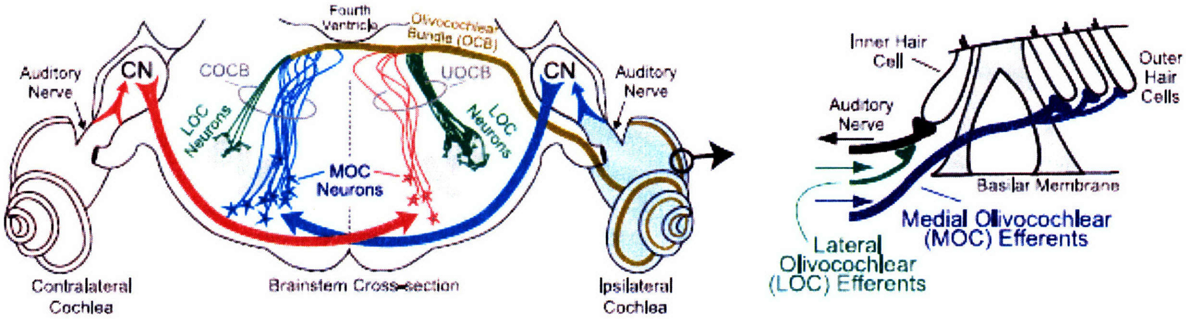

Figure 1. A schematized anatomic view of the olivocochlear reflexes to the right cochlea. *Left:* an outline of a transverse section of a cat brainstem showing the locations of lateral olivocochlear (LOC, green) and medial olivocochlear (MOC, blue or red) neurons. The pathways for the ipsilateral and contralateral MOC reflexes to the right ear are shown in blue and red, respectively, until they join the olivocochlear bundle (OCB, gold). The axons from LOC and MOC neurons form the OCB, which is composed of crossed (COCB) and uncrossed (UOCB) components. The COCB is accessible near the fourth ventricle. The S-shaped gray structure is the lateral superior olivary nucleus, and the gray structure medial to it is the medial superior olivary nucleus. *Right:* Schematic of the organ of Corti showing the main terminations of MOC neurons on outer hair cells and of LOC neurons on the dendrites of auditory nerve fibers.
(From Guinan, 2006, Ear & Hearing)

An overview of MOC effects on basilar membrane motion can be found in a review by Cooper and Guinan (2006). Medial efferents are thought to change the information carrying properties of auditory nerve fibers by acting on the OHCs to reduce the mechanical stimulus to IHCs. Electrical stimulation of medial efferents from the floor of the fourth ventricle in animals reduces the basilar membrane motion evoked by a tone at the characteristic frequency (e.g. Dolan et. al., 1997; Cooper and Guinan, 2003). Medial efferents synapse onto the base of OHCs. OHCs, because of their electrical motility, are thought to be the active elements involved in a positive feedback loop responsible for mechanical amplification of responses to sound (review: Dallos, 1992). In vitro, changes in the axial stiffness of isolated OHC were reported in response to acetylcholine (Ach) (Dallos et. al., 1997), which is also the Medial efferents' principal neurotransmitter. The stiffness changes occurred on a slow time scale that matches the time scale of the MOC "slow effect". But recently, it has been questioned whether the slow stiffness changes might be real or an artifact of the measuring method (Hallworth, 2007). Our measured SFOAE changes are more likely to be due to the MOC fast effect. The MOC fast effect is likely to be due to an OHC hyperpolarization induced by ACh and/or by the increased OHC synaptic conductance shunting the OHC receptor current.

Animal models of MOC efferent effects on cochlear mechanics form an important framework for theories on how the efferent system works to improve audition. But the body of work on humans remains in its infancy in comparison. In humans, studies have to employ non-invasive measurements that are thought to proxy the efferent-induced changes from within the cochlea. For this purpose, various kinds of otoacoustic emission (low-level sounds generated from within the cochlea in response to external sound stimuli) are used as the non-invasive vehicle to probe the changes in cochlear mechanics. In this study, we employed stimulus frequency otoacoustic emission (SFOAEs), cochlear "echoes" at the same frequency as the tonal stimulus used to generate the emission. A study on human SFOAEs measured from three different methods, each relying on a different cochlear phenomenon or signal processing technique, revealed little to no difference in the SFOAE measured – thus indicating that SFOAEs characteristics are cochlear phenomenon and not artifacts of measurement methodology (Kalluri and Shera, 2007). We use one of these methods, suppression by a tone at a nearby frequency, as a measure of the overall value of the SFOAE. As shown by Kalluri and Shera (2007) this gives approximately the same value for the SFOAE as the other available methods.

According to a theory first proposed by Kemp (1978), which was later formalized mathematically by Zweig and Shera (1995) and further developed by many others (e.g. Talmage et. al., 2000; Lineton and Lutman, 2003a, b, c), SFOAEs are generated in response to low-level sounds by linear reflections from densely-packed and randomly arranged mechanical inhomogeneities near the peak region of the basilar-membrane traveling wave. The inhomogeneities have been hypothesized to include irregular geometrical arrangements of hair-cells, irregular mechanical responses of electro-motile outer hair-cells, etc. The magnitudes and phases of SFOAEs contain valuable information on the cochlear mechanical response, and changes in the SFOAE vector in response to known efferent elicitors can be interpreted in terms of elicitor-induced changes in the cochlear mechanical response. In comparison to other types of OAEs, SFOAEs provide the most frequency specific probe since only a single tone frequency is needed to produce a SFOAE. Moreover, in contrast to other types of OAEs, the stimuli used to evoke SFOAEs produce insignificant MOC responses at stimulus levels commonly employed (Guinan et al. 2003). This is of great benefit since the activation of MOC efferents by the probe stimulus would confound the measure and obscure subsequent interpretation.

SFOAEs are physiologically susceptible to inhibition of electrohydromechanical processes within the cochlea for example due to activation of the MOC reflex (Guinan, 1990). That sound-induced changes in SFOAEs (ΔSFOAEs) can be interpreted as being due to MOC efferent activation arose from two lines of evidence in animal studies: 1) similar ΔSFOAEs are produced with localized brainstem shocks (Guinan, 1990). 2) sound-evoked activities similar to those found with MOC shocks disappeared when the MOC efferents were cut (e.g. Warren and Liberman, 1989a; Giraud et al., 1995; Kujawa and Liberman 2001). In addition to MOC-induced inhibition of SFOAEs, two-tone suppression of SFOAEs by an additional ipsilateral sound suppressor, usually at a near-by frequency, can also substantially reduce or eliminate the SFOAE (e.g. Kemp and Chum, 1980; Guinan, 1990). The changes in SFOAE resulting from MOC activation and two-tone suppression are fundamentally different in their origin and take place on different time scales (Guinan, 1990). MOC efferent fast-effects, which are the effects associated with inhibition of cochlear mechanics, operate on the order of hundreds of ms (Cooper and Guinan, 2003; Backus and Guinan, 2006) while two-tone suppression operates on the order 10 ms or less (Guinan, 1990). Hence, the MOC effects due to ipsilateral and bilateral elicitors can be measured in a post-elicitor time window starting with a delay from the elicitor offset that is long enough to allow for complete decay of two-tone suppression but an incomplete decay in the MOC effects.

To understand how SFOAEs can be used to study efferent effects in humans, we refer the reader to the vector diagram in Figure 2 below. The *Nominal Total Pressure* measured in the ear canal can be thought of as the sum of two complex components: a fixed amplitude *Sound Source Pressure* and the *SFOAE.* The *Nominal Total Pressure* vector is a function of time. If an additional sound-elicitor is able to elicit MOC efferent activity, a change in the magnitude and phase of the SFOAE can be induced, giving rise to a new emission sound $\mathrm{SFOAE}_{\mathrm{MOC}}$. This results in a new *MOC-inhibited Total Pressure* measured in the ear-canal. The vectorial difference between the measured *MOC-inhibited Total Pressure* and the *Normal Total Pressure* gives us a residual pressure equal to the elicitor-induced change in SFOAE (ΔSFOAE). In this thesis, we quantify the strength of the MOC reflex with the magnitude of the ΔSFOAE due to sound elicitors of MOC efferent activity.

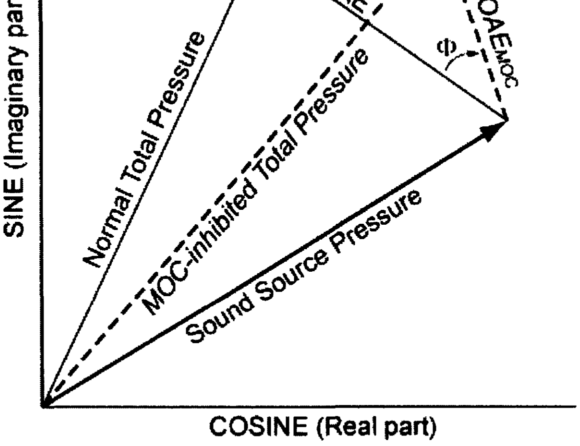

Figure 2. Vector diagram of MOC effects on sound pressures in the ear canal. The arrows are vectors in the complex plane such that the length of the arrow represents the magnitude and the direction of the arrow represents the phase. Before MOC stimulation, the *Sound Source Pressure* and the SFOAE summate to form the *Normal Total Pressure* in the ear canal. In the presence of an MOC effect, the SFOAE magnitude and phase are changed as shown by SFOAEMOC resulting in a new ear-canal sound pressure (*MOC-inhibited Total Pressure*). The change in the ear canal pressure shows the resulting change in the SFOAE, ΔSFOAE. Note that the angle ϕ shows the phase delay of SFOAEMOC from the SFOAE phase, opposite the sign convention used in the other figures of this thesis.

To date, there have been several hypotheses on the functional role of efferents – enhancement of dynamic range and/or improvement of signal to noise in the auditory periphery (Geisler 1974; Winslow and Sachs, 1998; Kawase et. al., 1993, etc.), sensory gating to mediate selective attention (e.g. Meric and Collet, 1994), and protection of the ear from acoustic overexposure (e.g. Reiter and Liberman, 1995). In this thesis, the role of MOC efferents in hearing is examined indirectly by learning basic properties of the MOC acoustic reflex system. Our main focus is on the frequency specificity of the human MOC system as determined by measurements of MOC-induced changes in SFOAEs as a function of elicitor frequency, laterality, and frequency content (Chapters 2, 3 and 4). There are two secondary focuses (1) The relative strengths of the ipsilateral and contralateral MOC effect at different regions along the cochlea (Chapter 5), and (2) binaural summation as a function of probe and elicitor frequency components (Chapter 6)

This thesis is divided into a total of 7 chapters with the first being this introduction and the last being the concluding chapter. The following section outlines the motivation and significance of each study.

III. Chapter Outline and Significance

Chapter 2: The Frequency Dependences of Contralateral, Ipsilateral and Bilateral Medial-Olivocochlear-Efferent Acoustic Reflexes in Humans

To understand the role of MOC efferents in hearing, basic physiological properties like its tuning need to be characterized. There are studies on MOC tuning in animals that suggest a narrow and frequency specific control offered by medial efferents (e.g. Liberman and Brown, 1986), but very little is known on humans. Also, the limited number of human studies on this topic focused solely on the contralateral reflex leaving the ipsilateral and bilateral responses an enigma (e.g. Chery-Croze et al., 1993; Norman and Thornton, 1993; Maison et al., 2000). This study provides the first measure of frequency specificity across all 3 lateralities of the MOC reflex in response to mid-level elicitors of 60 dB SPL as well as MOC-effect constant-response tuning curves for probe frequencies around 1 kHz.

Chapter 3: The Frequency Dependences of the Contralateral, Ipsilateral and Bilateral Medial-Olivocochlear-Efferent Acoustic Reflexes in Humans as Functions of Probe Frequency

Anatomical studies in the cat reveal that the innervation density of crossed and uncrossed efferent fibers vary along the length of the cochlea (Guinan et. al. 1984) while physiological studies in cats and guinea pigs reveal that MOC efferent tuning curves become sharper at higher frequencies (Liberman and Brown, 1986; Brown, 1988). Evidence of such property changes along the cochlear length prompted us to explore the frequency specificity of medial efferent reflex in humans at a lower (~0.5 kHz) and higher (~4 kHz) probe frequency regions than the 1 kHz region explored in chapter 2. In addition to investigating the extent of MOC effect along the frequency axis and for elicitor laterality, particular attention will be paid to the resulting magnitude and phase of the SFOAE during MOC activation and the implications of our results for understanding cochlear mechanics. This focus should provide more insight than most studies in the literature where only the magnitude of MOC-induced changes of otoacoustic emissions are noted and no attention is paid to changes in phase.

Chapter 4: The Effect of Elicitor Bandwidth on Contralateral, Ipsilateral and Bilateral Medial Olivocochlear Efferent Acoustic Reflexes in Humans at Low, Medium and High Probe Frequencies

Maison et. al. (2000) reported that for probe frequencies of 1 and 2 kHz, MOC-induced changes in otoacoustic emissions in humans increased with increasing bandwidths of contralateral elicitors, up to 2 octaves, the widest noise band tested. In contrast, in Chapter 2 of this thesis, significant contralateral efferent effects were found over a span of 5 octaves around a 1 kHz region in some individuals. Hence, it appears that the true extent of MOC bandwidth summation could be wider than the 2-octave limit of the previous human study. In this chapter, we investigated how MOC effects on SFOAEs near 0.5, 1 and 4 kHz are affected by changes in elicitor bandwidth over a 6.7 octave range, while the sound level of the elicitor was held constant. At each probe frequency, elicitor bandwidth series were run for contralateral, ipsilateral and bilateral elicitors centered on the probe frequency, and additionally, for 1 and 4 kHz, bandwidth series were done with the elicitor bands centered in a remote apical region well outside the critical band of the probe tone. The results show that, under all conditions, the MOC effect increased with increasing elicitor bandwidth. Hence, the feedback produced by the MOC efferent system to a specific cochlear location can be induced collectively from almost the entire cochlear length of both cochleae.

Chapter 5: Effects of Ipsilateral versus Contralateral Elicitors on Stimulus Frequency Otoacoustic Emissions as Functions of Elicitor Frequency Content

Anatomical studies in cats show that crossed and uncrossed MOC efferent fibers have different patterns along the length of the cochlea, but on the average, their ratio was 2:1 (Guinan et. al. 1984). Consistent with the anatomical data, physiological studies on cat and Guinea-pig MOC fibers revealed a 2:1 ratio in the number of MOC fibers that responded to the ipsilateral ear relative the number that responded in the contralateral ear (Liberman and Brown, 1986; Brown 1989; Robertson and Gummer, 1985). In contrast, in humans, the ipsilateral and contralateral reflex strengths were approximately equal when elicited with broadband noise (Backus, 2005). In this chapter, we systematically analyzed the ipsilateral/contralateral ratio of MOC effect on SFOAEs in humans as a function of elicitor frequency for probe tones near 1 kHz or 4 kHz. The results show that ipsilateral sounds produced significantly greater effects than contralateral sounds when the MOC elicitors were near the probe frequency. In contrast, MOC activity elicited with sounds at frequencies remote from the probe frequency produced ipsilateral and contralateral effects that were approximately equal. Thus, the ratio of ipsilateral to contralateral MOC effects may be as much determined by central processing as by the ratio of ipsilateral and contralateral efferent innervation in the periphery.

Chapter 6: Binaural Summation of Medial Olivocochlear Acoustic Reflexes in Humans

Physiological studies on guinea pigs found that contralateral sounds produced a greater increase in the firing of MOC fibers in the presence of an ipsilateral exciting sound than when the contralateral sound was presented alone, a phenomenon called binaural facilitation (Brown et. al. 1998). In humans, the MOC effect on SFOAEs near 1 kHz elicited by bilateral broad-band noise was well approximated by the sum of the effects produced by ipsilateral and contralateral noises presented separately, i.e. there was negligible binaural facilitation (Backus & Guinan, 2007). This chapter focuses on whether there is binaural facilitation in different probe frequency regions and with different elicitor frequencies relative to the probe frequency. The results show that binaural facilitation took place for 1 and 4 kHz probes when the response was activated by wide noise bands - indicating the importance of the medial efferent's bilateral organization for its role in audition under such hearing conditions

VI. References

Backus, B.C. (2005). 'Using Stimulus Frequency Otoacoustic Emissions to study basic properties of the human medial olivocochlear reflex,' Ph.D. Thesis, MIT, Chapter 2: 12-18.

Backus, B.C. and Guinan, J.J. Jr. (2006). 'Time-course of human medial olivocochlear reflex,' J. Acoust. Soc. Am. 119(5Pt1): 2889-2904.

Backus, B.C. and Guinan, J.J. Jr. (2007). 'Measurement of the distribution of Medial olivocochlear acoustic reflex strengths across normal hearing individuals via otoacoustic emissions,' J. Assoc Res. Otolaryngol. 8(4): 484-496.

Brown, M.C. (1989). 'Morphology and response properties of single olivocochlear fibers in the Guinea Pig,' Hear Res. 40(1-2):93-109.

Brown, M.C., Kujawa, S.G., Duca, M.L. (1998). 'Single olivocochlear neurons in the guinea pig. I.: Bilateral facilitation of responses to high level noises,' J. Neurophys. 79(6): 3077-3087.

Cooper, N.P. and Guinan, J.J. Jr. (2003). 'Separate mechanical processes underlie fast and slow effects of medial olivocochlear efferent activity,' J. Physiol. 548(Pt 1): 307-312.

Cooper, N.P. and Guinan, .J. Jr. (2006). 'Efferent-mediated control of basilar membrane motion,' J. Physiol 576: 49-54.

Chery-Croze, A., Moulin, A., Collet, L. (1993). 'Effect of contralateral sound stimulation on the distortion product 2f1-f2 in humans: Evidence of a frequency specificity,' Hear Res 68: 53-58.

Dallos, P. (1992). 'The active cochlea,' J. Neurosci. 12: 4575-4585.

Dallos, P., He, D.Z., Lin, X., Sziklai, I., Mehta, S., Evans, B.N. (1997). 'Acetylecholine, outer hair cell motility and the cochlear amplifier,' J. Neurosci. 17:2212-2226.

Darrow, K.N., Maison, S.F., and Liberman, M.C. (2006). 'Cochlear efferent feedback balances interaural sensitivity,' Nat. Neurosci. 9(12):1474-1476.

Dolan, D.F., Guo, M.H., Nuttall, A.L. (1997). 'Frequency-dependent enhancement of basilar-membrane velocity during olivocochlear bundle stimulation,' J. Acoust. Soc. Am. 102:3587-3596.

Galambos, R. 1956. Suppression of auditory activity by stimulation of efferent fibers to the cochlea. J. Neurophysiol. 19, 424-437.

Geisler, C.D. (1974). 'Hypothesis on the function of the crossed olivocochlear bundle,' J. Acoust. Soc. Am. 56: 1908-1909.

Groff J.A. and Liberman, M.C. (2003). 'Modulation of cochlear afferent responses by the lateral olivocochlear system: Activation via electrical stimulation of the inferior colliculus,' J. Neurophysiol. 90(5): 3178-3200.

Guinan J.J. Jr. (1996). 'The physiology of olivocochlear efferents,' In: Dallos P.J., Popper A.N., Fay, R.R. (eds.), The Cochlea. New York: Springer-Verlag, pp.435-502.

Guinan, J.J. Jr., Backus, B.C., Lilaonitkul, W., Aharonson V. (2003). 'Medial olivocochlear efferent reflex in humans: Otoacoustic emission (OAE) measurement issues and advantages of stimulus frequency OAEs', J. Assoc Res. Otolaryngol. 4(4):521-540.

Guinan, J.J. Jr., Warr, W.B., and Norris, B.E. (1984). 'Tonotopic organization of the olivocochlear projections from lateral and medial zones of the superior olivary complex,' J. Comp. Neurol. 226: 21-27.

Hallworth, R. (2007). 'Absence of voltage-dependent compliance in high-frequency cochlear outer hair cells,' J. Assoc. Res. Otolaryngol. 8(4):464-473.

Kalluri, R. and Shera, C. A. (2007). 'Comparing stimulus-frequency otoacoustic emissions measured by compression, suppression and spectral smoothing,' J. Acoust. Soc. Am. 122(6): 3562-3575.

Kawase, T., Delgutte, B., Liberman, M.C. (1993). 'Anti-masking effects of the olivocochlear reflex, II: Enhancement of auditory-nerve response to masked tones,' J. Neurophysiol. 70: 2533-2549.

Kemp, D.T. (1978). 'Stimulated acoustic emissions from within the human auditory system,' J. Acoust. Soc. Am. 64, 1386-1391.

Liberman, M.C., Brown, M.C. (1986). 'Physiology and anatomy of single olivocochlear neurons in cat,' Hear Res, 24:17-36

Lineton, B. and Lutman, M.E. (2003). 'Modeling the effect of suppression on the periodicity of stimulus frequency otoacoustic emissions,' J. Acoust. Soc. Am. 114(2): 859-870.

Lineton B., and Lutman, M.E. (2003). 'The effect of suppression on the periodicity of stimulus frequency otoacoustic emissions: experimental data,' J. Acoust .Soc. Am. 114(2): 871-82.

Lineton, B., and Lutman, M.E. (2003). 'A parametric model of the spectral periodicity of stimulus frequency otoacoustic emissions,' J. Acoust. Soc. Am. 114(2): 883-895.

Maison, S., Micheyl, C., Andeol, G., Gallego, S., Collet, L. (2000). 'Activation of olivocochlear efferent system in humans: influence of stimulus bandwidth,' Hear Res 140:111-125.

Meric, C. and Collet, L. (1994). 'Attention and otoacoustic emissions: a review,' Neurosci. Biobehavior. Rev. 18, 215-222.

Mountain, D.C. (1980). 'Changes in endolymphatic potential and crossed olivocochlear bundle stimulation alter cochlear mechanics.' Science. 210: 71-72.

Norman, M., Thornton, A.R.D. (1993). 'Frequency analysis of the contralateral suppression of evoked otoacoustic emissions by narrow-band noise,' Br J Audiol 27:281-289.

Reiter, E.R. and Liberman, M.C. (1995). 'Efferent-mediated protection from acoustic overexposure: Relation to :slow effects" of olivocochlear stimulation,' J. Neurophys. 73: 506-514.

Sridhar, T.S., Liberman, M.C., Brown, M.C., Sewell, W.F. (1995). 'A novel cholinergic 'slow effect' of efferent stimulation on cochlear potentials in the guinea pig,' J. Neurosci. 15: 3667-3678.

Siegel, J.H. and Kim, D.O. (1982). 'Efferent neural control of cochlear mechanics? Olivocochlear bundle stimulation affects cochlear biomechanical nonlinearity,' Hear. Res. 6:171-182.

Talmage, C.L., Tubis, A., Long, G.R., Tong, C. (2000). 'Modeling the combined effects of basilar membrane nonlinearity and roughness on stimulus frequency otoacoustic emission fine structure,' J. Acoust. Am. 108(6): 2911-2932.

Weiderhold, M.L. and Kiang, N.Y. (1970). 'Effects of electric stimulation of the crossed olivocochlear bundle on single auditory-nerve fibers in the cat,' J. Acoust. Soc. Am. 48: 950-965.

Winslow, R.L. and Sachs, M.B. (1988). 'Single tone intensity discrimination based on auditory nerve rate responses in backgrounds of quiet, noise and with stimulation of crossed olivocochlear bundle,' Hear Res 35: 165-190.

Zweig, G. and Shera, C. A. (1995). 'The origin of periodicity in the spectrum of evoked otoacoustic emissions,' J. Acoust. Soc. Am. 98(4): 2018-2047.

Chapter 2: The Frequency Dependences of Contralateral, Ipsilateral and Bilateral Medial-Olivocochlear-Efferent Acoustic Reflexes in Humans

Abstract

Various anatomical and physiological data from animals have lead to the view that single medial olivocochlear (MOC) efferent fibers provide frequency specific (i.e. cochlear-location specific) feedback to the cochlea, but there are few data from humans on this issue. The frequency specificity of acoustically-elicited MOC effects was studied in 7 human subjects (11 ears) using contralateral, ipsilateral, and bilateral tone and half-octave-band-noise elicitors at different frequencies to produce MOC activity. Stimulus-frequency otoacoustic emissions (SFOAEs) from 40-dB SPL tones near 1 kHz were used to quantify the MOC-induced change in the SFOAE, ΔSFOAE. The ΔSFOAEs induced by 60 dB SPL elicitors extended over a much wider elicitor frequency range than expected from animal MOC-fiber tuning curves. In some individuals significant ΔSFOAEs were elicited over the whole 5-octave elicitor-frequency range tested. The ΔSFOAE pattern was skewed with greater ΔSFOAEs for elicitor frequencies below the probe frequency. The elicitor frequency that produced the greatest ΔSFOAE ranged from 1 octave below to ½ octave above the probe frequency. In contrast to the wide frequency range of ΔSFOAE from mid-level elicitors, MOC-effect tuning curves (TCs) were frequency specific with Q10s of ~2, sharper than the MOC-fiber TCs found near 1 kHz in cats and guinea pigs. For all elicitor lateralities, TCs from tone elicitors were V-shaped with the tip frequency displaced from the probe frequency, commonly to a lower frequency. With half-octave-band noise, TCs were wider and sometimes had tips at a frequency above the probe. In summary, the MOC acoustic reflex appears to have sharp, offset, tuning at low sound levels and widens considerably at moderate levels with sounds below the probe frequency eliciting the greatest ΔSFOAEs. The data are consistent with an anti-masking role of MOC efferents, especially to reduce masking by mid-level noises at frequencies below the probe (listening) frequency.

Abbreviations

BBN	Broadband Noise (0.1-10kHz)	**PTS**	Permanent Threshold Shift
BF	Best Frequency	**SFOAE**	Stimulus Frequency Emission
BM	Basilar Membrane	**SNR**	Signal-To-Noise Ratio
CF	Characteristic Frequency	**STD**	Standard Deviation
MOC	Medial Olivocochlear	**ΔSFOAE**	normalized complex change in the SFOAE,
NBN	Half-Octave Noise		
OAE	Otoacoustic Emission	**TC**	Tuning Curves
OHC	Outer Hair Cell	**TTS**	Temporary Threshold Shift

I. Introduction

Despite the vast body of knowledge on Medial Olivocochlear (MOC) efferent anatomy and physiology, many aspects of the system's inner workings and a consensus on the functional roles of the MOC efferents remain uncertain. This study focuses on the frequency selectivity of the ipsilateral, contralateral and bilateral MOC acoustic reflexes in humans at probe frequencies near 1 kHz. Knowledge of MOC frequency selectivity should aid in assessing the role of the MOC efferents in audition.

During acoustic stimulation, MOC efferents provide a neural signal from the central nervous system to the inner ear that reduces the gain of the cochlear amplifier by altering the properties of the electro-motile outer hair cells (OHC) thereby reducing the mechanical stimulus to the inner hair cells. Animal data show that the cochlear amplifier sharply tunes the basilar membrane's (BM) mechanical response to sound giving rise to auditory nerve excitations that are highly frequency specific. In animals, the firings of single MOC neurons exhibit a frequency-tuning sharpness in response to low-level sound stimulus that almost matches their afferent counterparts (Liberman and Brown, 1986; Brown, 1989). In addition, Liberman and Brown (1986) reported that cat MOC efferents innervate a region spanning 0.1 to 1 octave on the tonotopic map that included, or was near, the place where afferents with the same characteristic frequency (CF) originate. These findings from animals have led to the conception that MOC efferents provide narrow, frequency-specific inhibition, i.e. narrow-band sound is thought to evoke MOC activity that inhibits cochlear responses within a narrow frequency range around the sound frequency.

Studies on human MOC frequency specificity were initiated with the conceptual framework provided by the animal results. However, unlike animal experiments, human experiments have to rely on non-invasive methods. A common approach has been to elicit MOC activity with contralateral sound and to employ the change in some evoked Otoacoustic Emission (OAE) amplitude as a measure of the strength of MOC inhibition. Evoked otoacoustic emissions are soft sounds in the ear canal that are generated within the cochlea in response to external sound stimuli. Provided that the stimulus levels used do not induce middle-ear-muscle contractions, changes in OAEs due to acoustic stimulation are likely to originate within the cochlea. The rationale for interpreting acoustically induced changes in OAEs as being due to efferents stem from two lines of evidence. First, direct electrical stimulation of MOC efferents produces changes in OAEs (Mountain, 1980; Siegel and Kim, 1982; Guinan 1990), presumably because MOC fibers synapse directly on OHCs and thereby change the mechanical properties of the cochlea (A wide range of evidence indicates that OHCs are instrumental in producing the gain of the cochlear amplifier—Dallos, 1992). Second, acoustic stimulation produces similar effects on auditory–nerve responses as the effects produced by direct electrical stimulation of MOC fibers, and furthermore, these effects disappeared when the OC bundle was cut (Warren and Liberman, 1989a, b).

To date, only a few studies on the frequency specificity of the human MOC acoustic reflex exist (Veuillet et al., 1991; Chery-Croze, et al. 1993; Norman and Thornton, 1993; Maison et al., 2000). However, it is unclear how much the results are contaminated by probe-induced MOC responses, middle ear muscle (MEM) contractions (Guinan et al, 2003) and noise-induced bias in the amplitude measure (Backus, 2007). Moreover, previous studies were limited to measuring only contralateral MOC effects to avoid the obscuring effects produced by two-tone suppression of the OAE by an ipsilateral elicitor. Hence, there are no reports on ipsilateral or bilateral MOC frequency specificity in humans. Another limitation in almost all previous studies of MOC frequency specificity in humans is that data were for noise-burst elicitors even though tones would be expected to provide the most frequency specific activation of MOC efferents. Thus, these studies left the true extent of MOC frequency specificity unknown.

In this study, we measured MOC effects in the cochlear frequency region near 1 kHz as a function of elicitor frequency and elicitor laterality. The elicitors of MOC activity were mid-level (60 dB SPL) pure tones, or half-octave noises (NBN), presented contralaterally, ipsilaterally, or bilaterally, over a range of 5 octaves around the probe tone. Stimulus-frequency otoacoustic emissions (SFOAEs) from 40-dB SPL tones near 1 kHz were used to quantify the MOC-induced change in the SFOAE, ΔSFOAE. This measurement design avoids most of the issues that have obscured the interpretation of earlier studies (Guinan et. al, 2003). We also measured MOC-effect tuning curves (TCs). Overall, we found that MOC effects show a degree of sharp tuning but the peak effect was not for elicitors centered at the probe frequency as was expected. One interpretation of these results is that the MOC efferents may function as an anti-masking system especially suited for masking produced by sound-frequency-regions below the probe (or listening) frequency.

II. Methods and Analysis

A. Subjects

The present study used data from 11 ears from 7 adult subjects (4 female, 3 male; ages: 22 to 33, average: 27.5) with clinically normal hearing thresholds in both ears (within 20 dB re. ANSI pure tone threshold at octave frequencies from 250 Hz to 4 kHz). Measurements were conducted in a sound-proof room. A warning light was automatically turned on before each stimulus presentation and the subject was instructed to sit still during the time that the light was on and sounds were presented. For this study, a pool of 8 subjects was screened and 1 subject was rejected. Subjects were rejected if they did not pass all of the following criteria:

1) The magnitude of the ΔSFOAE elicited by a 60 dB SPL bilateral broadband (0.1-10kHz) noise (BBN) was at least 0 dB SPL[1].
2) No change in ear-canal sound pressure was found during the middle-ear-muscle (MEM) test (explained below).
3) The subject was able to stay awake and sit still during the experiment.
4) The subject returned to complete the study.

B. Acoustic Stimuli

As a probe sound to evoke SFOAEs in both ears, a 40-dB SPL continuous tone[2] selected at a frequency within ±10% of 1 kHz was presented bilaterally through the earphones of 2 Etymotic ER10C acoustic assemblies. For each subject, a probe frequency was selected that: (1) was at least 100 Hz away from any spontaneous OAE with magnitude above -10 dB SPL (this was done to avoid possible entrainment – van Dijk, et. al., 1988), and (2) produced the largest ΔSFOAE magnitude to a 60 dB SPL, contralateral BBN (so that the signal/noise ratio (SNR) criteria could be reached with the smallest number of stimulus repeats).

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[1] Backus and Guinan (2007) found that for probe frequencies near 1 kHz, a ΔSFOAE elicited by 60 dB SPL contralateral BBN elicitors could be measured in all 25 of 25 subjects tested, although not all SFOAE frequencies within a subject produced measurable ΔSFOAE magnitudes. For SFOAE frequencies for which ΔSFOAE magnitudes were measurable, no prevailing trend across subjects in the properties of ΔSFOAE magnitudes was observed: The distribution of ΔSFOAE magnitudes near 1 kHz was reasonably approximated by a Gaussian distribution (mean ~30%; std. = 10%). So according to this study, MOC effects quantified by ΔSFOAE magnitudes should be measurable in all subjects albeit perhaps not at the exact same frequency. We know of no reason why our rejection of subjects with low ΔSFOAE magnitudes would bias our results, although this cannot be ruled out.

[2] Contralateral tones at the probe frequency presented at 40 dB SPL were found to be weak elicitors of efferent response (Guinan et al., 2003).

To elicit MOC activity, a 60 dB SPL tone or NBN was presented ipsilaterally, contralaterally or bilaterally for 2500 ms. Preceding the elicitor was a 0.5 s onset period from which the baseline response was measured, and following the elicitor was a 2 s period for recovery. The resulting stimulus repetition period was 5 s (Fig. 1A). 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 NBN elicitor. Elicitors were presented at frequencies from 2.5 octaves below to 2.5 octaves above the probe frequency, in half-octave steps, and were presented in a randomized order to avoid bias. In each subject, data gathering runs of tone or NBN elicitor frequency series were interleaved to minimize possible long-term variation in responses and thereby allow direct comparisons of the results.

The SFOAE preceding the MOC elicitor, referred to as the baseline SFOAE, was measured from the vectorial difference of the ear-canal sound pressure from the 40 dB SPL probe tone with and without a 60 dB SPL suppressor tone at 110 Hz below the probe frequency[3]. The baseline SFOAE vector was measured separately from the ΔSFOAE vector in runs in which the suppressor was presented for 500 ms every 1 second (Fig. 1B). For both suppressor-tones and MOC-elicitors, 5-ms rise/fall cosine ramps were introduced at the presentation edges to minimize spectral splatter. Consecutive elicitor or suppressor presentations had opposite polarities so that upon averaging their acoustic waveforms would cancel leaving a residual measure equal to the amount of induced change in the SFOAE vector.

Calibrations of the acoustic output from the two sound sources in each ER10C acoustic assembly were done (using the microphone in the ER10C) at the beginning of every data gathering session and frequently within a session. Noise bursts were made to be spectrally flat by applying these calibrations.

Measurements in a given subject sometimes took months to complete. Preliminary studies showed that measurements of both SFOAEs and elicitor-induced changes in SFOAE were remarkably consistent over the months involved. Examples of ΔSFOAE data sets taken months apart are shown in Appendix A. For each subject, the SFOAE measurements had standard deviations (STDs) that were at least an order of magnitude less than the STDs of the elicitor-induced changes in SFOAE. Thus, when expressing the MOC effect as the change in the SFOAE vector, normalized by the baseline SFOAE amplitude, the variability introduced by the baseline SFOAE measurement is small.

C. Measurement Analysis

Frequency-series data-gathering runs were typically done in even-numbered blocks that averaged 4-10 artifact-free responses at each elicitor frequency. Response pairs were rejected as being contaminated with artifacts (usually from subject movement) when the difference between one pair of responses and the next pair exceeded a criterion (pairs were used because the signs of the elicitor and suppressor sounds were reversed on alternate trials). Multiple data blocks were vectorially averaged to achieve response averages with $N \geq 60$ stimulus repetitions. The averaged waveforms were then heterodyned to obtain the complex waveform of the response at the probe frequency. Details of the heterodyning method and specification of the frequency domain filtering can be found elsewhere (Guinan et al, 2003).

The complex amplitude of the ear canal sound pressure at the probe frequency, P(t), is the sum of the probe-tone and the evoked SFOAE(t) complex amplitude. An MOC elicitor, or a suppressor, can induce a

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[3] Backus and Guinan (2007) found that the SFOAE obtained using these parameter values can underestimate the true SFOAE amplitude, i.e. the suppressor produces only 80-100% suppression. The variability in the *degree* of underestimation could have increased the standard error of our group averages. However, underestimation of the SFOAE magnitude did not affect the shape of the MOC effect curves because, for a given ear, all points were normalized by the same SFOAE measure.

change in the SFOAE and thereby change P(t). Changes in the SFOAE(t), ΔSFOAE(t), were calculated from P(t) by the vectorial difference between P(t) and $P_{baseline}$ where $P_{baseline}$ is the vector average of P(t) between 50-450 ms, i.e. the average P(t) before the onset of the suppressor or MOC elicitor (see Guinan 2003 for more detail). The MOC-induced change was then expressed as a fraction of the SFOAE by dividing ΔSFOAE(t) by the baseline SFOAE vector. That is,

$$\Delta\text{SFOAEn}(t) = \frac{P(t) - P_{\text{Baseline}}}{\text{SFOAE}} = \frac{\Delta\text{SFOAE}}{\text{SFOAE}} \qquad \text{(eq. 1)}$$

Where,

$P(t)$ = the complex heterodyned measurement, and $0 < t < 5s$.
$P_{Baseline}$ = the vectorial average of P(t), and $0.05 < t < 0.45s$
SFOAE = the complex baseline stimulus frequency otoacoustic emission evoked by the probe tone.
ΔSFOAEn(t) = the change in the SFOAE normalized by the baseline SFOAE.

In the equation above, SFOAE(t) and ΔSFOAE(t) were the raw, un-normalized values and ΔSFOAEn(t) was the normalized value. In all of the remaining, we will use only the normalized values and will drop the "n" so that henceforth ΔSFOAE(t) = ΔSFOAEn(t) of above. A vector diagram of the ear canal sound pressures can be found in Figure 2. An example of ΔSFOAE(t) is shown in Figure 3.

Normalized ΔSFOAE(t) data were vectorially averaged in either a 0.1 s "during-elicitor" time window ending 50 ms before the end of the elicitor (for contralateral elicitors), or a 0.1 ms "post-elicitor" time window starting at 50 ms after the end of the elicitor (for ipsilateral and bilateral elicitors and, for comparison, also for contralateral elicitors). Averaging in the post-elicitor window avoids two-tone-suppression effects of the probe that can be evoked by ipsilateral and bilateral elicitors, but at the expense of capturing the MOC effect during its decay. Two-tone-suppression is absent for contralateral elicitors so the contralateral ΔSFOAE(t) can be averaged from a during-elicitor window near the end of the elicitor presentation which allows us to capture the maximum MOC effect elicited. The noise floor estimate was obtained from averaging the ΔSFOAE(t) in a time-window of the same duration as the (during or post-elicitor) data-analysis time window, but positioned such that the end of the noise time window was 50 ms before the end of a stimulus repetition period.

To minimize biasing effects due to noise[4], data from a given ear and elicitor type were included for analysis only if the maximum effect from the elicitor frequency series had an SNR of at least 3 (~9.5 dB). The 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.

D. Middle-ear-muscle (MEM) contraction test

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[4] Consider a simplified 2-dimensional scenario of a signal vector in the complex plane in the presence of a Gaussian noise whose joint distribution over the real and imaginary parts have zero mean and σ standard deviation. When the signal amplitude is much higher than the noise, the effect of the noise on the signal estimation is negligible. However, at low signal to noise ratios, the amplitude and phase estimation of the signal could be dominated by noise. At the extreme of having no signal present, we would still measure a non-zero amplitude due to the noise. Hence, bias increases as SNR decreases.

A MEM test was performed on each subject to ensure that the MEMs were not activated at the stimulus levels used. In this test, 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. MOC efferents act only on the OAEs from within the cochlea, while MEM contractions can change both the sound from the source (by changing the middle-ear impedance) and the OAE (by changing middle-ear transmission properties). However, MOC-induced changes in the SFOAE will not be detected if the SFOAE is fully suppressed, so the 65 dB SPL suppressor[5] was added to suppress the SFOAE. On the other hand, MEM contractions will still affect the middle-ear impedance seen at the tympanic membrane resulting in a change in the sound pressure in the ear canal even in the presence of the suppressor. So with this paradigm, only MEM contractions produce a change in the sound pressure at the SFOAE probe frequency. Thus, 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.

E. Tuning curves of MOC effect

Tuning curves (TCs) of ΔSFOAE magnitudes were obtained as equal response contours derived from identical elicitor frequency sweeps done at different elicitor levels. The "best frequency" (BF) was taken to be the frequency that produced the largest MOC-induced change in the SFOAE from the lowest-level elicitor frequency series, and the magnitude of the ΔSFOAE at this BF was used as the criterion response for the equal response contour. Then the elicitor frequencies that yielded the criterion ΔSFOAE were calculated by interpolation of the ΔSFOAE obtained at higher elicitor levels.

To derive the TCs, frequency sweeps 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 contraction in many subjects. Data for a particular elicitor level were included in the derivation of TCs only if the maximum ΔSFOAE magnitude in that frequency series had an SNR ≥ 3 (~9.5 dB). All elicitor frequency series for a TC used the same 40 dB SPL probe tone. To see if using a 40 dB SPL probe influenced the result, in one subject the elicitor-level-and-frequency series were repeated with a 20 dB SPL probe tone (data in Appendix C). ΔSFOAE

F. Determining the statistical significance of variations across parameters

To determine the statistical significance of the variations of ΔSFOAE 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 ΔSFOAE magnitudes passed the Lillifores test for normality. If they did not pass, the Friedman non-parametric two-way ANOVA was used. Statistical significance was accepted at the 0.05 level. The data were compared to a control data set that measured the response under the Null-hypothesis of no MOC effect (i.e. in the absence of a MOC-elicitor). The control data were the noise floor measurements taken from a time-window of the same duration as the (during or post-elicitor) data-analysis time window, but positioned such that the end of the noise time window was 50 ms before the end of a stimulus repetition period.

G. Testing the hypothesis of ΔSFOAE magnitude symmetry along the frequency axis

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[5] Tones at 65 dB SPL were not found to induce MEM contractions.

For a data set consisting of ΔSFOAE magnitudes as a function of elicitor center frequency from different subject ears, we wanted to determine whether the pattern of effects was asymmetric in elicitor frequency relative to the probe frequency. That is, we wanted to know if magnitudes of the ΔSFOAEs from elicitor frequencies below the probe frequency were larger than those from above the probe frequency to a statistically significant degree. To determine if the ΔSFOAE frequency response curve averaged across subjects was statistically asymmetric, we first determined the sampling distribution for the skewness statistic, b_l (b_l explained in detail below), under the Null hypothesis that the distribution was symmetric about the probe frequency. For this, we employ a bootstrap with replacement method (Efron and Tibshirani, 2000). The sampling protocol for constructing the null-hypothesis skewness statistics, $b_{l,NULL}$, is as follows.

Under the Null hypothesis of symmetry, the ΔSFOAE magnitude for an elicitor frequency at a given number of octaves above the probe frequency, $MOC_{NULL}(f)$, is the same as the ΔSFOAE magnitude for an elicitor at the same number of octaves below the probe frequency. In mathematical terms:

$$\Delta SFOAE_{NULL}(f) = \Delta SFOAE_{NULL}(-f), \quad \text{for all } f \qquad \text{(eq. 2)}$$

Where,

f = the elicitor frequency in octaves relative to the probe frequency

Hence, we can create a trial Null distribution from the data actually obtained for each elicitor frequency by randomly choosing for $\Delta SFOAE_{NULL}(f)$ either from the sets of pooled subject data $\Delta SFOAE_{ACTUAL}(f)$ or $\Delta SFOAE_{ACTUAL}(-f)$. Sampling was done with replacement. From this trial Null distribution we can calculate a trial value of the skewness statistic, $b_{l,NULL}$. If this is done a large number of times, we obtain the bootstrapped distribution of $b_{l,NULL}$, which is a symmetrical distribution about the origin. The actual result is taken to have statistical significance if its measured b_l falls outside the 95% occurrence interval of $b_{l,NULL}$. That is, if the probability $\hat{P}$ that the absolute value of $b_{l,NULL}$ is equal to, or greater than, b_l is less than 0.05. As an example, the bootstrapped Null distribution for the skewness coefficient b1, from the during-elicitor contralateral NBN data is shown in Figure 4.

We note that the probability $\hat{P}$ is an estimate and the number of bootstrapping trials, M, will affect the accuracy of $\hat{P}$. M should be large enough for the probability $\hat{P}$ to converge within some predefined allowable error range. Details of the derivation for the minimum required M is in the Appendix D. To obtain an error level (arbitrarily chosen at 0.01) 95% of the time ($\alpha=0.05$) for $P=0.05$, $M \geq 3719$ would suffice. For all bootstrapping analysis, we set M arbitrarily at 4000 which exceeds the minimum M estimate.

To determine the skewness statistic, b_l, we expressed the elicitor frequency as octaves relative to the probe frequency. So that subjects with larger overall ΔSFOAE magnitudes would not be weighted more in the averages, the ΔSFOAE magnitude vs. frequency curve of each subject was equalized such that for each subject, the sum across frequency of the equalized MOC effects equaled unity. That is,

$$\sum_{i=1}^{n} MOC_E(F_i) = 1, \qquad \text{(eq. 3)}$$

and,

$$MOC_E(F_i) = \frac{MOC(F_i)}{\sum_{i=1}^{n} MOC(F_i)} \qquad \text{(eq. 4)}$$

where:

F_i = the ith elicitor frequency in octaves re. the probe frequency,

$MOC(F_i)$ = the MOC effect at the ith elicitor frequency,

$MOC_E(F_i)$ = the equalized MOC effect at the ith elicitor frequency,

N = the number of elicitor frequencies.

We next employ a skewness measure (b_1) as the test statistic for asymmetry[6]. The statistic is defined as follows:

$$b_1 = \frac{\sum_{i=1}^{n} (F_i - \bar{F})^3}{(n-1)s^3} \qquad \text{(eq. 5)}$$

and

$$\bar{F} = \sum_{i=1}^{n} \left(\overline{MOC}_{E,E}(F_i) \times F_i \right) \qquad \text{(eq. 6)}$$

$$\overline{MOC}_{E,E} = \frac{\frac{1}{m}\sum_{j=1}^{m} MOC_{E,j}(F_i)}{\sum_{i=1}^{n}\left(\frac{1}{m}\sum_{j=1}^{m} MOC_{E,j}(F_i) \right)} \qquad \text{(eq. 7)}$$

$$s = \sqrt{\left[\frac{1}{n-1} \sum_{i=1}^{n} (F_i - \bar{F})^2 \right]} \qquad \text{(eq. 8)}$$

where:

$\bar{F}$ = the weighted mean of F using $\overline{MOC}_{E,E}(F_i)$ as weights.

$\overline{MOC}_{E,E}(F_i)$ = the equalized averaged $MOC_E(F_i)$ across subjects.

j = the subject index (1,..,m).

m = the number of subjects.

s = the estimated standard deviation of F using $\overline{MOC}_{E,E}(F_i)$ as weights.

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[6] Any perfectly symmetric function about the sample mean would yield a zero coefficient of skewness. When the skewness is positive and statistically significant, the data are spread out more towards the left of the mean. If skewness is negative, the data are spread more towards the right.

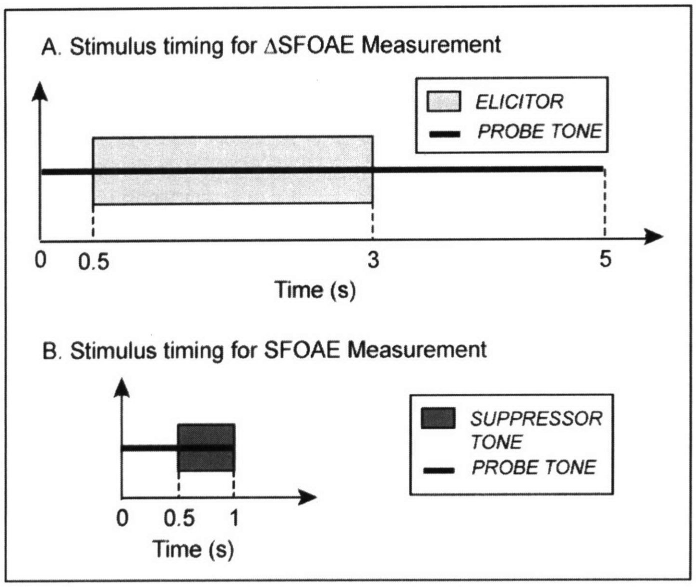

Figure 1. Temporal presentation of stimuli. **A**. For the measurement of the elicitor-induced ΔSFOAE, there was an initial delay of 0.5 s to establish the baseline response, then a 2.5 s tone or noise burst to elicit MOC activity, followed by a 2 s recovery period. This stimulus pattern was repeated every 5 s with the polarity of the elicitor alternated so that upon averaging the measurements, the elicitors would cancel leaving a residual pressure equal to elicitor-induced ΔSFOAE. **B**. For the SFOAE measurement, there was an initial delay of 0.5 s to establish the baseline response, then a 0.5 s suppressor tone at 110 Hz below the probe frequency. This stimulus pattern was repeated every 1 s with the polarity of the suppressor alternated.

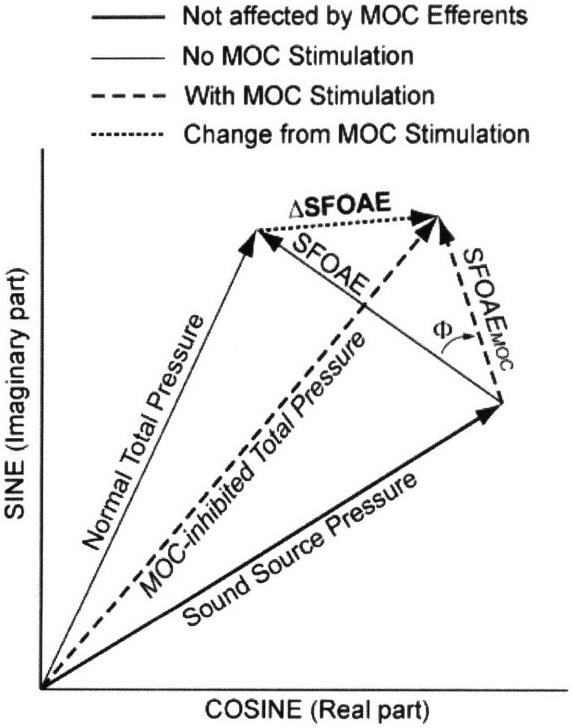

Figure 2. Vector diagram of MOC-elicitor effects on sound pressures in the ear canal. The arrows are vectors in the complex plane such that the length of the arrow represents the magnitude and the direction of the arrow represents the phase. Before stimulation by the MOC-elicitor, the *Sound Source Pressure* and the SFOAE summate to form the *Normal Total Pressure* in the ear canal. In the presence of an MOC-elicitor the SFOAE magnitude and phase are changed as shown by $\text{SFOAE}_{\text{MOC}}$ resulting in a new ear-canal sound pressure (*MOC-inhibited Total Pressure*). The change in the ear canal pressure shows the resulting change in the SFOAE, ΔSFOAE.

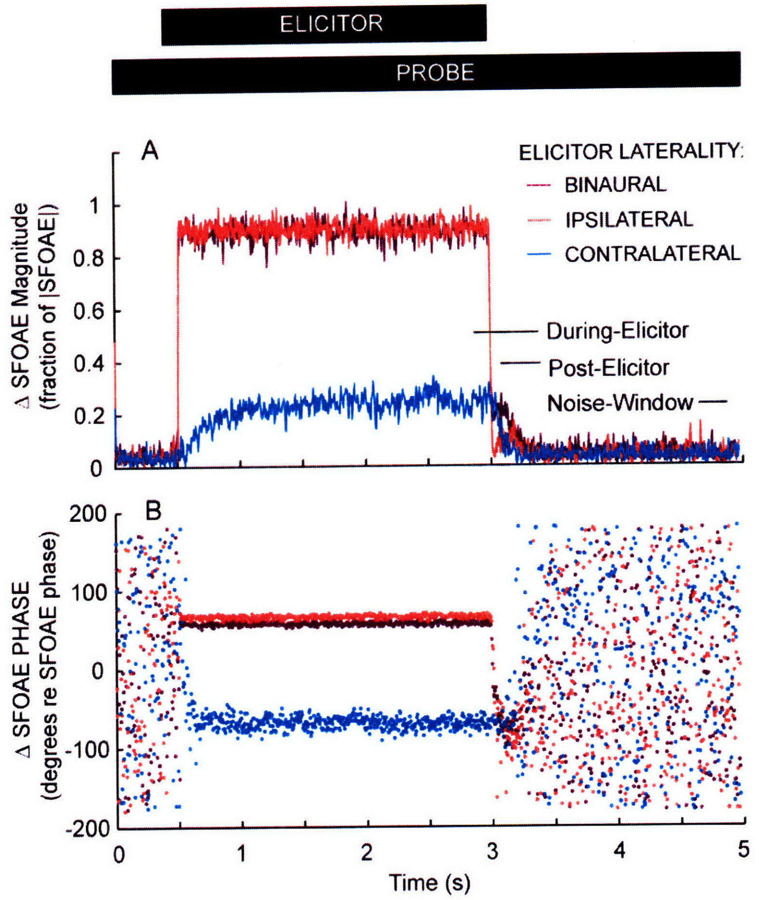

Figure 3. An example of the Magnitude (A) and Phase (B) of the ΔSFOAE(t) elicited by Bilateral (Purple), Ipsilateral (Red) or Contralateral (Blue) half-octave noise elicitors during a stimulus repetition (Top Panel above A). The complex ΔSFOAE(t) was obtained from the ear-canal sound pressure by (1) heterodyning at the probe-tone frequency (1100 Hz), (2) vector averaging the result over a baseline interval (0.05-0.45 s), (3) subtracting this baseline average, at each time point, from the heterodyned response to yield the change in the SFOAE from the baseline and (4) normalizing this measure by dividing it with the SFOAE vector estimated from a separate experiment. The elicitor had a center frequency a half-octave below the probe frequency and was presented from 0.5 to 3 s. The sharp rise and fall in the magnitude at the start and end of the ipsilateral and bilateral elicitor presentations were due to two-tone suppression of the probe-tone SFOAE by the elicitor. This suppression decayed quickly ($\tau < 10$ ms) so that ΔSFOAE in the post-elicitor window (3.05-3.15 s) was presumed to be free of suppression (see Methods). The approximate equality of the phase for all three lateralities at the time of the post-elicitor window is consistent with the suppression having died away so the phase of the remaining MOC effect is shown. Also note, that the 5000ms duration appears to be long enough to allow for the MOC effect to have completely decayed before the next stimulus presentation. This can be seen by the completely random phase at the end of the run (B), which signifies the absence of any statistically significant remnants of a MOC effect signal, i.e. the ear-canal sound pressure had decayed back to its baseline value so the phase value was the phase of the baseline noise.

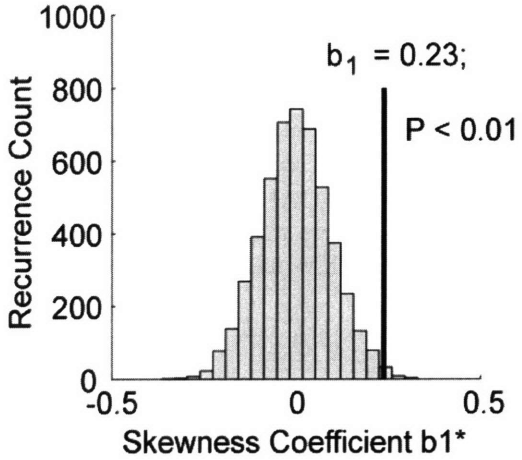

Figure 4. Histogram of the skewness coefficient obtained from the ΔSFOAE magnitude data (11 ears) from contralateral NBN elicitors by bootstrapping under the Null hypothesis of symmetry. **In this case, the actual skewness coefficient of the original data set was 0.24 and is significantly different from zero ($\hat{P}$=0.0066). The conclusion is that the original ΔSFOAE magnitude distribution was significantly skewed relative to the probe frequency.**

III. Results

ΔSFOAE magnitudes (|ΔSFOAEs|) as a function of elicitor frequency were measured on 11 ears of 7 subjects using both tone and noise-band elicitors at 60 dB SPL. Elicitor-frequency functions were obtained for contralateral, ipsilateral, and bilateral elicitors; we will first consider the contralateral data. Only contralateral stimulation allows |ΔSFOAE| measurements to be made *during* the elicitor so that the near-maximum effect of the MOC-elicitor can be measured. Figure 5 shows examples from two subjects of typical |ΔSFOAEs| for NBN elicitors, and the corresponding MEM-test results, both as functions of elicitor frequency. Note that most of the |ΔSFOAE| data are well above the noise level, whereas the values from MEM-test runs are close to, or less than, the mean noise level. For all of the stimulus frequencies and levels used in this study, MEM tests were done and showed no evidence of MEM contractions.

A. Frequency specificity of |ΔSFOAE|

|ΔSFOAE| as a function of contralateral elicitor frequency were quantified from the vector average of the ΔSFOAE in a 100 ms "during elicitor" window that ended 50 ms prior to the end of the elicitor. This window captured the |ΔSFOAE| near its maximum, and since the elicitor was in the contralateral ear, there are no suppressive effects. Figure 6 shows the individual during-elicitor |ΔSFOAEs| for all ears (N=11) as functions of contralateral elicitor frequency for tone (Fig. 6A) and NBN (Fig. 6B) elicitors. There were significant inter-subject differences in the frequency patterns of individual |ΔSFOAEs| (multi-dimensional ANOVA: $P_{NBN} < 10^{-3}$, $P_{Tone} < 10^{-3}$). However, no consistent left or right ear dominance was observed; on the average, there is no significant difference between the left and right ear pools (from 4 Subjects with both left and right ear measurements, multi-dimensional ANOVA: $P_{NBN}=0.29$, $P_{Tone}=0.86$). Considering this, the right and left ear data were pooled in making Figure 6.

During-elicitor |ΔSFOAEs|, averaged across ears as a function of elicitor frequency relative to the probe frequency, are shown in Figure 6, bottom. Elicitor frequency had a significant effect on the average |ΔSFOAEs| (Multi-dimensional ANOVA: $P_{NBN} < 10^{-3}$, $P_{Tone} < 10^{-3}$). The average during-elicitor contralateral |ΔSFOAE| was significantly different from the noise floor over a wide range of elicitor frequencies: for NBN, elicitor frequencies between -1.5 to +1.0 octaves relative to the probe frequency (~2.5 octave span), and for tone elicitors, frequencies between -1.5 to- 0.5 octaves relative to the probe frequency (~1 octave span). The frequencies at which significant |ΔSFOAEs| were found are indicated by asterisks in Figure 6. At the frequencies with significant |ΔSFOAEs|, the average values were at least 60% of the average maximum effect. Considering individual ears, the exact range of significant effects along the frequency axis varied across ears. At least 1 subject had significant |ΔSFOAEs| at the 0.05 level over the entire 5 octave span tested (e.g. Fig. 5C). There was large inter-subject variation in the elicitor frequency that showed the largest |ΔSFOAE| (Fig. 6A, B) so that, in the average across subjects of tonal |ΔSFOAEs|, there was a broad peak region between 0.5 octaves and 1.5 octaves below the probe frequency. The peak region was even broader for the |ΔSFOAEs| of NBN because larger |ΔSFOAEs| were elicited at frequencies at and above the probe frequency than for tone elicitors.

An interesting feature of the data is that elicitor frequencies lower than the probe frequency usually produced larger |ΔSFOAEs| than elicitor frequencies above the probe frequency (Fig. 6). This pattern of asymmetry across elicitor frequency was true for both tone and NBN elicitors (asymmetry hypothesis testing (see methods): $b1=0.53$, $P_{b1} < 10^{-3}$ for tones; $b1=0.23$, $P_{b1}=6.6\times10^{-3}$ for noise). Furthermore, the skewness was more pronounced in response to tones ($b_{1,Tone} > b_{1,NBN}$).

In summary, on average, near steady-state contralateral |ΔSFOAEs| exhibited a surprising asymmetry with elicitor frequencies below the probe frequency being the most effective and the asymmetry being more pronounced with tone than with NBN elicitors. In addition, the range of significant effects along the frequency axis was wider with NBN than with tone elicitors. Over these ranges, the average |ΔSFOAEs| were at least 60% of the maximum.

B. Frequency specificity of |ΔSFOAE| from contralateral, ipsilateral and bilateral elicitors.

Measurements of |ΔSFOAEs| produced by ipsilateral and bilateral elicitors cannot use a during-elicitor window because while an elicitor is present in the ipsilateral ear, it produces suppression (called two-tone suppression) of the SFOAE. Measurements of ipsilateral and bilateral |ΔSFOAEs| were made using data from a post-elicitor window that captured the |ΔSFOAE| after the complete decay of elicitor-induced suppression but before the MOC effect had decayed completely (see Methods). Since 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 |ΔSFOAE| is affected by measuring it in the post-elicitor window.

Figure 7, left, shows comparisons of the average during-elicitor and post-elicitor |ΔSFOAEs| from contralateral tone and NBN elicitors. There were few qualitative differences between the results from the post-elicitor versus the during-elicitor windows. Both had similar shapes and similar positive skews towards frequencies below the probe ($b1_{Tone}$=0.53 and $b1_{NBN}$=0.23 for during elicitor; $b1_{Tone}$=0.38 and $b1_{NBN}$=0.19 for post elicitor). However, for the post-elicitor data the signal decayed into the noise floor at some frequencies that showed a statistically significant |ΔSFOAE| in the during-elicitor data. Thus, the post-elicitor data for ipsilateral and bilateral |ΔSFOAEs| should yield useful information on the shape of the MOC effects versus elicitor frequency and on the effect skew, but may underestimate the amplitude and significance range of the MOC effect.

Figure 7, right, shows the |ΔSFOAEs| from contralateral, ipsilateral and bilateral elicitors as measured in the post-elicitor window. There were large inter-subject variations (multi-dimensional ANOVA: $P_{NBN} < 10^{-3}$; $P_{Tone} < 10^{-3}$) but no statistical difference between the average |ΔSFOAEs| in the left and right ear (multi-dimensional ANOVA: P_{NBN}=0.61; P_{Tone}=0.56). Thus, to increase the significance, data from the right and left ears were pooled in Figure 7. For these data, the elicitor frequency had a significant effect for both tone elicitors (ANOVA: $P_{Bi} < 10^{-3}$, $P_{Ipsi} < 10^{-3}$, $P_{Contra} < 10^{-3}$) and NBN elicitors (ANOVA: $P_{Bi} < 10^{-3}$, $P_{Ipsi} < 10^{-3}$, $P_{Contra} < 10^{-3}$). The frequencies at which significant |ΔSFOAEs| were found are indicated by asterisks in Figure 7. For ipsilateral and bilateral elicitors the range of significant |ΔSFOAEs| went from -1.5 to +0.5 octaves, or more, relative to the probe-tone frequency. Within the frequency ranges of significant |ΔSFOAEs|, the average |ΔSFOAEs| were all at least 60% of the maximum effect. On individuals, the range of significant |ΔSFOAEs| varied between ears. For all lateralities and elicitor types, at least 1 ear showed significant |ΔSFOAEs| over the entire 5 octave range tested. For the data of Figure 7, the largest |ΔSFOAEs| in individuals' responses to bilateral and ipsilateral elicitors were found over a wide frequency region that included the probe frequency.

|ΔSFOAE| asymmetry was significant for all lateralities and had a pattern similar to the contralateral during-elicitor data shown earlier. On average, elicitor frequencies lower than the probe frequency produced larger |ΔSFOAEs| than elicitor frequencies above the probe frequency. Moreover, 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 the corresponding hypothesis test results are shown in Table 1.

In general, the average bilateral |ΔSFOAE| at each elicitor frequency was greater than either the ipsilateral or the contralateral effect. Differences in the |ΔSFOAEs| across the ipsilateral, contralateral and bilateral elicitor lateralities were statistically significant (ANOVA: $P_{NBN} < 10^{-3}$; $P_{Tone} < 10^{-3}$). The average ipsilateral |ΔSFOAE| was approximately equal to, or greater than, the contralateral |ΔSFOAE| such that the ratio of their relative strengths appeared to vary as a function of elicitor frequency. The ratio of Ipsi/Contra |ΔSFOAE| was greatest at the probe frequency. A more detailed analysis of the Ipsi/Contra comparative effects will be covered separately in a later chapter.

In summary, the |ΔSFOAEs| from contralateral, ipsilateral and bilateral elicitors measured in the post-elicitor window are similar in most respects to the contralateral |ΔSFOAE| measured in the during-elicitor window. These |ΔSFOAEs| were asymmetric with elicitor frequencies below the probe frequency being the most effective and the asymmetry being more pronounced with tone elicitors than with NBN elicitors. Although the |ΔSFOAEs| measured in the post-elicitor window are less than they would be during the elicitor, statistically significant effects were measured over a wide range of elicitor frequencies.

C. MOC-effect tuning curves

In many auditory studies, frequency selectivity is characterized by tuning curves, 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. The drawback of TCs, in the present context, is that calculation of a TC requires frequency-response data over many sound levels. Since the data for a typical frequency-response plot took at least 5 hours to obtain, we were able to obtain the data necessary to calculate TCs only for six ears (3 subjects) and only on two ears were we able to obtain enough data to calculate a TC for each elicitor laterality. Since 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 TCs from contralateral elicitors because, as noted earlier, only MOC effects from contralateral elicitors can be measured during the elicitor presentation. Figure 8 shows data from the two subjects with a TC from each elicitor window: during-elicitor or post-elicitor. |ΔSFOAEs| from elicitor frequency series at several elicitor levels are shown for the during-elicitor window (Fig. 8, top), and for the post-elicitor window (Fig. 8, middle). The TCs derived from these data are shown in Figure 8, bottom. The TCs from the two subjects were qualitatively similar in that they were V-shaped, centered below the probe frequency and had similar frequency-spans at the highest elicitor levels tested. For the five TCs obtained with contralateral tones (3 subjects), the BF, the frequency with the largest |ΔSFOAE| at the lowest elicitor level, was 0.5 or 1 octave below the probe frequency (Q10 values are found in table 2).

The sharpness of tuning for auditory-nerve fibers and MOC neurons is conventionally quantified by a dimensionless measure Q10 - which is the bandwidth/BF ratio where BF is the best frequency and the bandwidth is measured from the TC at a level 10 dB above the "threshold" at the BF[7]. For the TCs from contralateral elicitor tones, the Q10 values ranged from 1.3 to 3.3 (table 2).

Since the ipsilateral and bilateral MOC effects had to be quantified from the post-elicitor window, it is of interest to get a sense of how tuning in the post-elicitor and the during-elicitor windows differ. As seen in Figure 8, the contralateral TCs from these two windows were very similar. For the 2 subjects of Figure 8,

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[7] The best frequency is normally the frequency with the lowest threshold response. We have arbitrarily used 30 dB SPL for the "threshold" and as BF used the frequency with the largest response to a 30 dB SPL elicitor.

the Q10 of the during-elicitor TC was slightly higher than the Q10 of the post-elicitor TC, which could be due to the lower SNR in the post-elicitor window.

In summary, contralateral |ΔSFOAE|-TCs to tonal elicitors were generally V-shaped with Q10 values that were significantly greater that 1, which is the average Q10 of MOC-fiber TCs around 1 kHz in anesthetized cats. The tip frequency of the human MOC-effect TC was always offset to below the probe frequency for these contralateral elicitors.

D. Contralateral, ipsilateral and bilateral tone-elicitor TCs

TCs from ipsilateral and bilateral (and contralateral, for comparison) elicitors were calculated from the post-elicitor window. As seen above, the post-elicitor window is expected to yield TCs with lower SNRs but with shapes similar to TCs of |ΔSFOAEs| during the elicitor (see Fig. 8). Figure 9 shows the TCs to contralateral, ipsilateral and bilateral tone elicitors for 3 subjects. Most notably, the TC tip frequency was always displaced from the probe frequency. Except for the right-ear, ipsilateral TC of subject 181 where the tip frequency was above the probe frequency, all TCs had tip frequencies that were either 0.5 octave or 1 octave below the probe frequency. The TC tip could be located at different frequencies for TCs of different lateralities, or for the left and right ears of the same subject (Fig. 9). The mean Q10 values for contralateral, ipsilateral and bilateral tone elicitors were all near 2 (respectively: 2.0 ±0.3; 2.0 ±0.4; and 2.1 ±0.4). The Q10s are given in table 2.

In summary, TCs from contralateral, ipsilateral and bilateral tone elicitors shared the same important features: a tip frequency that was displaced from the probe frequency, usually below, and Q10 values near 2.

E. NBN-elicitor TCs.

In the two subjects extensively tested, TCs were obtained with NBN elicitors in addition to the tone-elicitor TCs shown above. The NBN TCs, more often than the tone TCs, had tip frequencies that were located above the probe frequency (Fig. 10B, C, F). NBN-elicitor TCs were generally wider than the corresponding tone-elicitor TCs (Figure 10). Q10 values are summarized in table 3. Widening of TCs with NBN elicitors was more dramatic with bilateral and contralateral elicitors than with ipsilateral elicitors. For TCs from NBN elicitors compared to TCs from tone elicitors, the positions of the TC-tip frequencies and the increased bandwidth for elicitors above the probe are consistent with the pattern observed earlier that NBN elicitors show less skew than tone elicitors (Figure 6).

In summary, in the two subjects tested, TCs to NBN elicitors were generally wider than TCs to tones and sometimes NBN elicitors produced shifts in the TC tip to frequencies above the probe.

Elicitor Laterality:	**Bilateral**		**Ipsilateral**		**Contralateral (Post-Elicitor)**		**Contralateral (During-Elicitor)**	
Elicitor Type:	**Tone**	**NBN**	**Tone**	**NBN**	**Tone**	**NBN**	**Tone**	**NBN**
Skewness Factor, $\mathbf{b_1}$	0.41	0.29	0.25	0.19	0.38	0.19	0.53	0.23
$\hat{P}_{b_1}$	**$<10^{-3}$**	**$<10^{-3}$**	**$4.00\text{x}10^{-3}$**	**$3.06\text{x}10^{-2}$**	**$<10^{-3}$**	**$<10^{-3}$**	**$<10^{-3}$**	**$6.60\text{x}10^{-3}$**

Table 1: Summary of asymmetry measures for |ΔSFOAEs| from bilateral, ipsilateral and contralateral 60-dBSPL elicitors. Skewness was quantified by the skewness factor, $\mathbf{b_1}$, where zero signifies perfect symmetry about the mean, positive skewness factors indicate a response bias towards lower frequencies (left of the mean) and vice versa. The significance of each skewness factor being different from 0 was tested against a bootstrapped distribution under the null hypothesis of symmetry. The resulting probability that the distribution is symmetric is given as: $\hat{P}_{b_1}$. Significance was taken at a 0.05 P-value.

Subject	**Post-Elicitor**			**During Elicitor**
	Bilateral Tone	**Ipsilateral Tone**	**Contralateral Tone**	**Contralateral Tone**
S179R	1.83	1.58	2.74	3.29
S181R	3.14	2.61	1.69	2.33
S216R	2.00	2.23	-	1.97
S179L	-	1.22	-	1.25
S181L	-	2.39	-	-
S216L	1.52	-	-	1.33
Mean	**2.13**	**2.01**	-	**2.04**
Std. err.	**(±0.35)**	**(±0.26)**	-	**(±0.38)**
$P_{t\text{-test}}$ (Null Hypothesis:Q_{10}=1)	**$4.96\text{x}10^{-2}$**	**$1.80\text{x}10^{-2}$**	-	**$4.93\text{x}10^{-2}$**

Table 2: Q10 values from TCs to contralateral, ipsilateral and bilateral tone elicitors. Left column shows subject number and ear. '-' indicates that the measurement was not available due to poor SNR. TCs are shown in Figures 7 and 8.

	Post-elicitor, Bilateral		**Post-elicitor, Ipsilateral**		**During Elicitor, Contralateral**	
Subject	Tone Q10	NBN Q10	Tone Q10	NBN Q10	Tone Q10	NBN Q10
S179R	1.83	0.53	1.58	1.22	3.29	1.47
S181R	3.14	2.49	2.61	2.49	2.33	1.18

Table 3. Summary of comparative Q10 values of TCs to tone and NBN elicitors to the ipsilateral, contralateral and bilateral ears. Left column shows subject number and ear. TCs are shown in Figure 9.

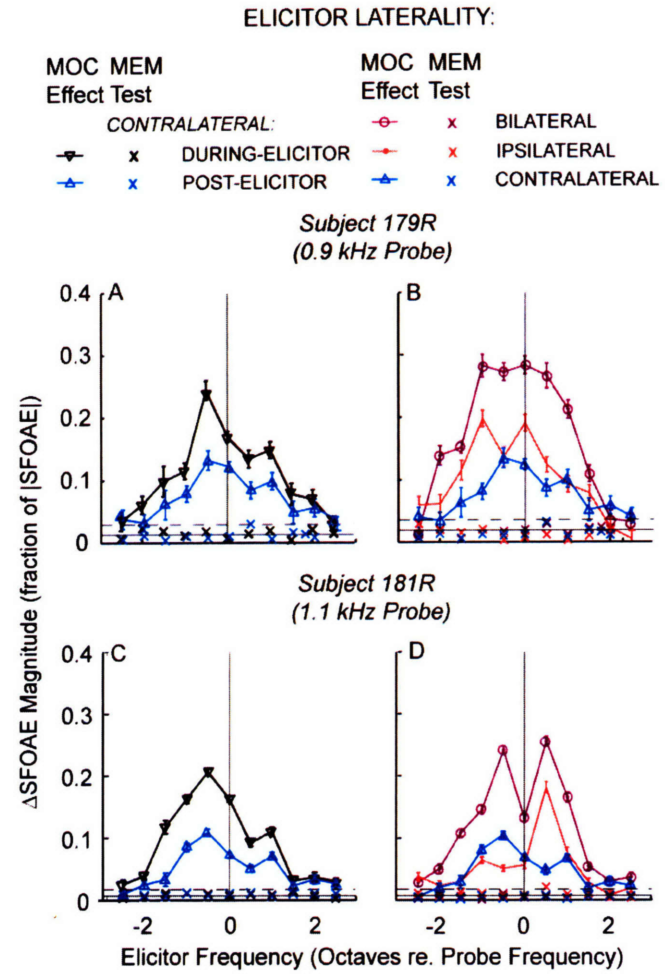

Figure 5. Examples of |ΔSFOAEs| from 2 subjects as a function of half-octave noise elicitor frequency in the absence of MEM contractions. Error bars are 1 standard error of the mean. Contralateral |ΔSFOAEs| were measured in either a during-elicitor window (black: −∇−) or a post (blue: −Δ−) elicitor window while both the ipsilateral (red: —) and bilateral (purple: −O−) |ΔSFOAEs| were measured in the post-elicitor window. 'X' are results from the MEM-contraction test; the measures are generally within 2 standard deviations (std). of the noise floor (Black: solid (mean), dash (2 std. above the noise mean).

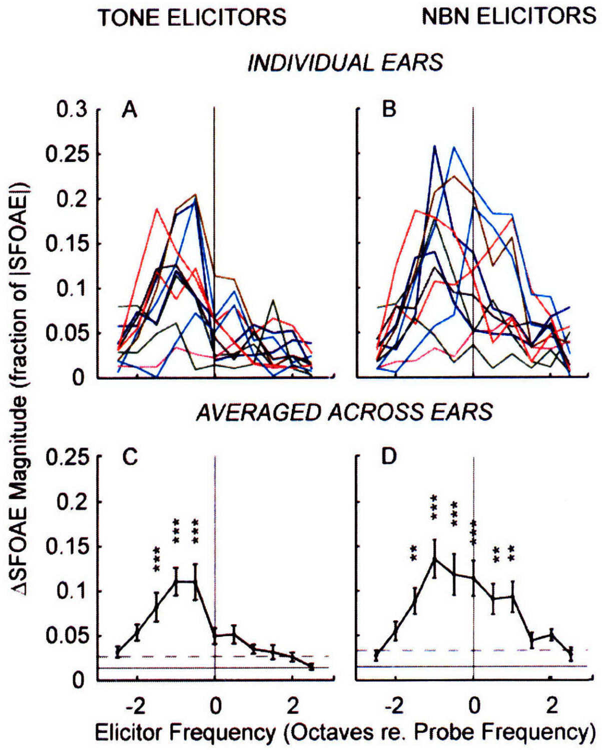

Figure 6: |ΔSFOAEs| in response to NBNs and tones showed wide SFOAE amplitude inhibition capabilities along the frequency axis and a significant offset towards frequencies below the probe frequency. Error bars are 1 standard error of the mean. |ΔSFOAEs| of 11 Ears from 7 Subjects as functions of tone (A, C) and NBN (B, D) elicitor frequency are overlaid (1st Row) and averaged (2nd Row). The horizontal black line (C, D) corresponds to the average noise mean. Dotted line represents 2 standard deviations above the noise mean. The average |ΔSFOAEs| (2nd Row) were significantly above the noise floor between -1.5 to -0.5 octaves for tone elicitors and between -1.5 to 1 octaves for noise elicitors. Significant values are marked with '*' ($P \leq 0.05$), '**' ($P \leq 0.01$), '***' ($P \leq 0.001$). Tone-elicited |ΔSFOAEs| exhibited a greater positive skew than NBN-elicited |ΔSFOAEs|. Skewness coefficients are summarized in table 1.

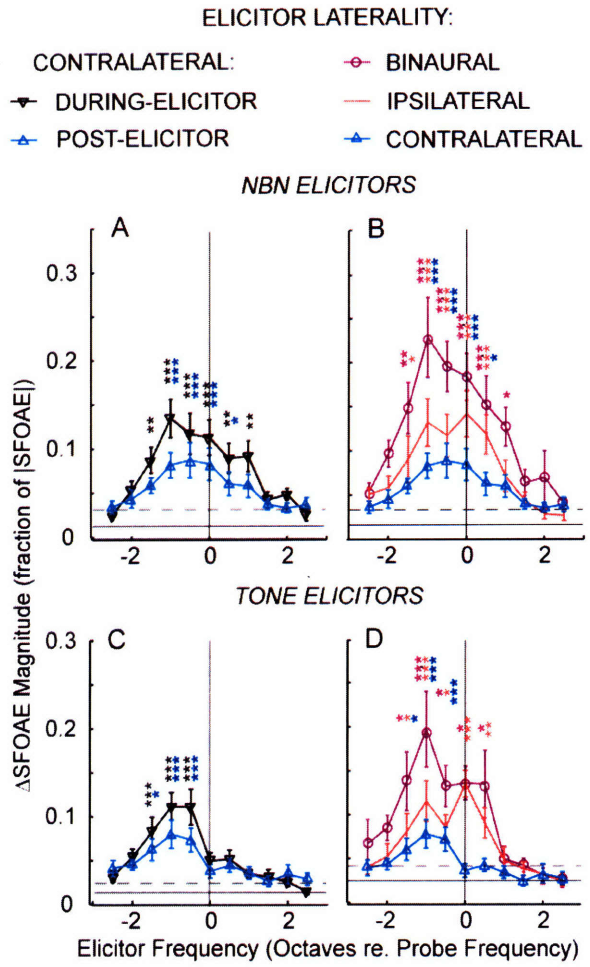

Figure 7. |ΔSFOAEs| to ipsilateral (red: —), contralateral (blue: Δ and black: ∇) and bilateral (purple: O) tone (bottom) and NBN (top) elicitors as functions of elicitor frequency. Error bars are 1 standard error of the mean. Elicitors were 60 dB SPL half-octave noise bands (NBN) (A, B) or tones (C, D). Data were vectorially averaged over 0.1 s time windows: 2.85-2.95 s for the during-elicitor measure; 3.05-3.15 s for the post-elicitor measure. Noise measures were vectorially averaged over 4.85-4.95 s. Multiple comparisons were done with a Bonferroni correction. Statistically significant values are marked with '*' ($P \leq 0.05$), '**' ($P \leq 0.01$), '***' ($P \leq 0.001$). Skewness coefficients are summarized in table 1.

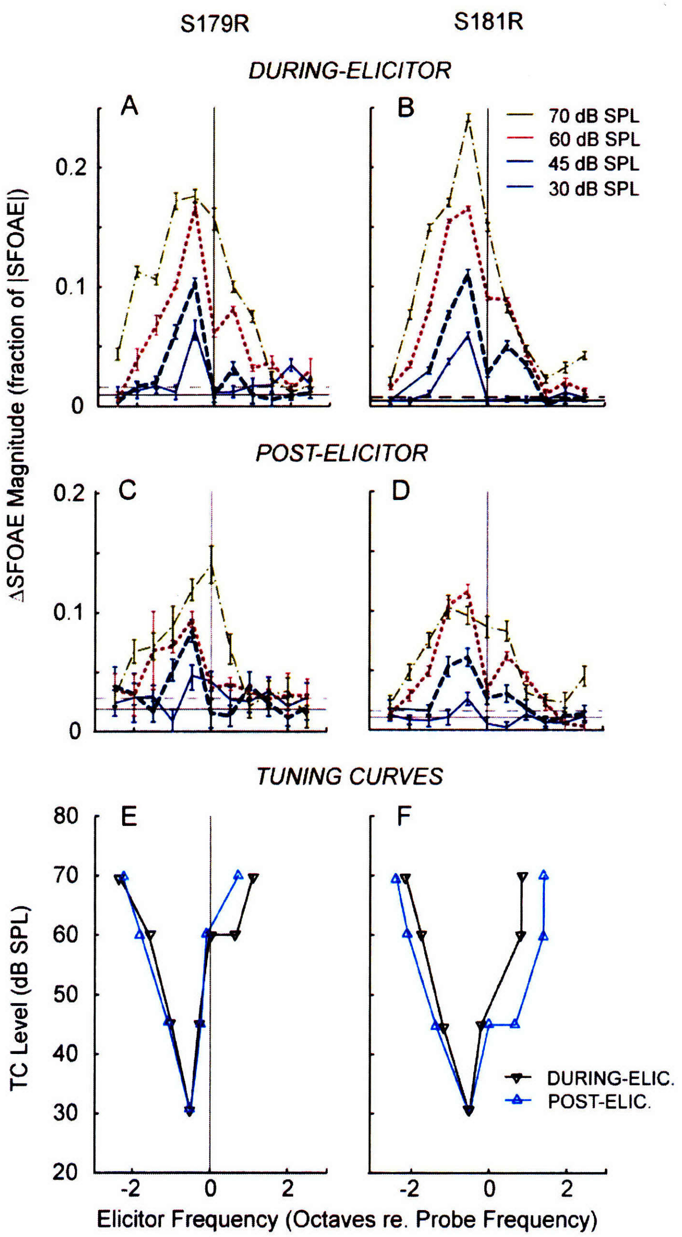

Figure 8. |ΔSFOAEs| from elicitor tone-frequency series done at different sound levels (A-D) and the tuning curves (TCs) derived from them (E, F) in 2 subjects (columns). Error bars (A-D) are 1 standard error of the mean. |ΔSFOAEs| were averaged from a 0.1 s during-elicitor (2.85-2.95ms) window (A, B) or from a 0.1s-post-elicitor (3.05-3.15ms) window during the MOC effect's decay (C, D). The |ΔSFOAEs| corresponding to the tips of the TCs (E, F) had SNRs of at least 9.5 dB. The derived TCs and calculated Q10 values are summarized in Table 2.

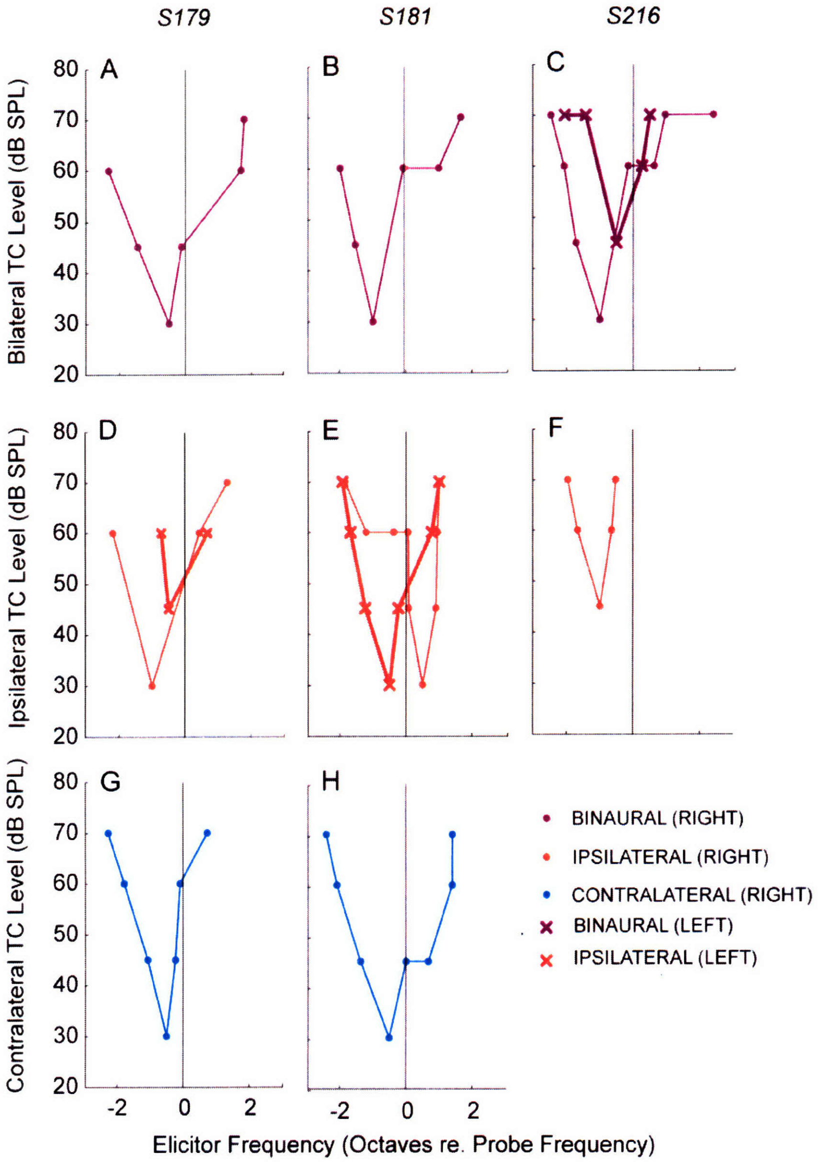

Figure 9. Tuning curves from bilateral (purple, 1st Row), ipsilateral (red, 2nd Row), and contralateral (blue, 3rd Row) tone elicitors from the left (x) and right (•) ears of 3 subjects. Data were averaged in a 0.1 s post-elicitor window (3.05-3.15 s).The |ΔSFOAEs| corresponding to the tips of the TCs had SNRs of at least 9.5 dB. Q10 values are summarized in table 2.

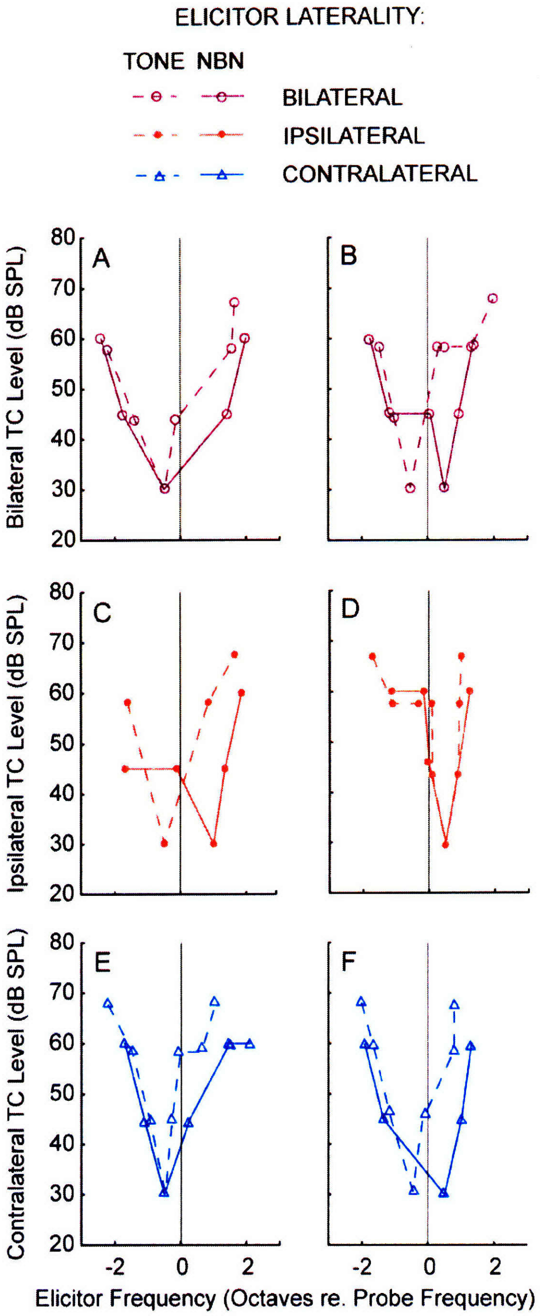

Figure 10: In the two subjects tested, NBN-MOC-effect-TCs to bilateral (purple: O), ipsilateral (red: —) and contralateral (blue: Δ) elicitors were wider than their tone-MOC-effect-TCs (black: ∇) counterparts and there were shifts in the TC tip frequency. Ipsilateral and bilateral TCs were from data averaged the post-elicitor window (3.05-3.150 s) while the contralateral TCs were from data averaged the during-elicitor window (2.85-2.95 s). The |ΔSFOAEs| corresponding to the tips of the TCs had SNRs of at least 9.5 dB. Q10 values are summarized in table 3.

IV. Discussion

Overview and Methodological Considerations

When we started this work, we hypothesized that narrow-band sounds would elicit significant MOC activity only when they were close in frequency to the probe tone, and that the peak MOC effect would be when the elicitor frequency was the same as the probe frequency (e.g. Veuillet et al., 1991; Chery-Croze et al., 1993). Our data show moderately sharp tuning (Q10 ~ 2), but surprisingly, with the peak |ΔSFOAEs| either below (usually) or above (sometimes) the probe frequency. Additionally, our data show that significant |ΔSFOAEs| can be produced by elicitors far in frequency (as much as 2.5 octaves) from the probe frequency.

There are several main limitations on the strength of the conclusions that can be drawn from our data. One limitation is that the data are only from 11 ears from 7 subjects, and the data showed considerable heterogeneity (Fig. 4A). Although most of our results are statistically significant, including the wide range of elicitor frequencies that showed |ΔSFOAEs| and the skewness of these data, it is not clear that our data captured the true distribution of the whole population, or, for instance, whether MOC tuning might fall into several categories based on differences in tuning. In addition, subjects were rejected from the study if they did not meet all of the selection criteria (See Methods A), which included a minimum criterion (0 dB SPL) for the |ΔSFOAE| elicited by bilateral sound. Though possible, we do not think this selection criterion introduces a significant bias: In an earlier study (Backus and Guinan, 2007), no evidence of MOC-effect property differences were found when measured from a population of normal-hearing subjects that were not selected based on the level of their |ΔSFOAEs|. A second limitation is that the data were only for elicitors near 1 kHz. The shapes of auditory-nerve TCs and the pattern of MOC innervation vary across the length of the cochlea and so we might expect the pattern of |ΔSFOAEs| to also vary across the cochlea. A third limitation is that we do not know the correspondence between the MOC effects as measured by changes in SFOAEs (or changes in any OAE) and the inhibition that is produced in auditory-nerve fibers. Despite these limitations, our conclusions paint a new picture of MOC effects in which the largest MOC effect is not necessarily at the frequency of the probe, and MOC effects can be elicited by moderate-level sounds remote in frequency from the probe frequency.

It is important to consider whether our results are biased by poor SNRs. The |ΔSFOAEs| from an ear were included in the averaging pool only if the maximum |ΔSFOAEs| from contralateral, ipsilateral and bilateral elicitors each had an SNR that was equal to, or greater than, 9.5 dB. At this SNR level, the amount of noise-induced bias in the amplitude measurement is almost negligible (Backus, 2007). In contrast, |ΔSFOAEs| measured for elicitor frequencies near the edge of the range had much lower SNRs and may be biased by their low SNRs. Nonetheless, off-peak data that were statistically above the noise floor were seen over a wide elicitor frequency range. The accuracy of these measurements may be improved with more experimental repeats. Therefore the reported elicitor frequency range over which the |ΔSFOAE| was statistically significant provides a lower bound for the true range of MOC effects at the probe frequency. Low SNRs could result in an underestimation of the |ΔSFOAE| skew since the magnitude of data points with low signals would be biased upward by the noise. We minimized different biases across lateralities and elicitor bandwidths (i.e. tone vs. NBN) by interleaving these measurements in each subject so that the resulting noise floors were not statistically different. Note that the contralateral effect showed the greatest skew even though it had the lowest overall signal magnitude and SNR compared to the ipsilateral and bilateral effects, which indicates that the noise floor of our data was low enough to not obscure the skewness.

There are several methodological issues regarding the construction of MOC-effect TCs. First, the TCs were constructed from series in which the elicitor frequencies were half an octave apart, so a TC's tip frequency was only a stepped estimate of the actual best frequency. Second, SNR may affect the TC in several ways. The lowest-sound-level elicitor-frequency series was used for the TC only if its maximum |ΔSFOAE| passed the SNR criterion of 3. An SNR of 3 insures that the maximum point was significantly above the noise, but does not insure that it was significantly above the other points from the same frequency series. Thus, if two frequencies yielded almost equal |ΔSFOAEs|, small amplitude changes, perhaps due to noise, may determine which frequency is selected as the tip frequency. If the two elicitor frequencies with almost equal |ΔSFOAEs| are above and below the probe frequency, then a small response change can produce a large and dramatic shift in the TC tip frequency. A second SNR issue is that poor SNRs could bias the determination of Q10s. Although the tip-frequency point has a good SNR, the adjacent TC frequency points are determined by interpolation and the lower-level point in this interpolation may not have a good SNR. A low SNR would make this point show an artificially higher amplitude that would make the resulting TC wider. We think this was not much of a problem. For instance, although this SNR bias would decrease Q10's measured from the post-elicitor window compared to Q10's from the during-elicitor window, no decrease is found in our data for contralateral elicitors (Table 2).

Another issue is that we have obtained TCs only for a small number of subjects and mostly for tone elicitors. The individual TCs may not be representative of the MOC effects across many subjects. Our results showed tip frequencies that were mostly below the probe frequency, some were above, but none had tip frequencies at the probe frequency (Note: We only measured elicitor frequencies at ½ octave steps). This should not be taken to indicate that there was little or no MOC effect for elicitors the same frequency as the probe. For 40 dB SPL ipsilateral elicitors, tone or NBN, the maximum |ΔSFOAE| in the average across our 11 ears, was for elicitors at the probe frequency (Fig. 6, right).

Relationship of our results to previous reports

The frequency selectivity of contralateral efferent effects on otoacoustic emissions had been explored in previous work on humans. Veuillet et. al. (1991) employed evoked-otoacoustic emissions (EOAEs) from 1 kHz tone pips as their probe and reported that changes in the EOAE could be elicited by 50-dB SPL contralateral noise-bands centered within a 2 octave range about the 1 kHz probe (10 Subjects). But in contrast to our results, Veuillet et. al. reported the maximum efferent reflex when the noise band was centered at the probe frequency. Chery-Croze et al (1993) used distortion-product otoacoustic emissions (DPOAEs) on 8 subjects and reported that in general, the MOC-induced inhibition in DPOAE level in individual subjects appeared to take place for a restricted range of contralateral narrow noise-bands (55 dB SPL) centered between 0.75 and 1.5 kHz (0.4 octaves below to 0.6 octaves above their 1 kHz 2fi-f2 probe) and on the average, the maximum induced change was obtained with a narrow-band noise centered above the 1 kHz probe at 1.25 kHz. These human studies did not rule out the presence of MEM effects, or adequately deal with possible biases from poor SNRs, complications that could obscure the data and confound interpretation (Guinan et. al., 2003; Backus, 2007). Furthermore, given the high probe stimulus levels used by Vieullet et. al. (1991) and Chery-croze et. al. (1993), it is very likely that the probe itself was a potent elicitor of MOC activity (Guinan et. al, 2003). As a result, it is difficult to determine the origin of the differences between their results and ours.

One interesting feature of our data is that we found significant |ΔSFOAEs| elicited by tones. Previous studies e.g. Maison et. al., 2000; Guinan et. al., 2003), including our own, found only weak MOC effects produced by tones, possibly because these studies looked for MOC effects at the frequency of the elicitor tone.

There are no reported measurements of MOC-effect TCs in humans for comparison with our current measures. In cats, Q10s from fibers with BFs near 1 kHz, both auditory-nerve and MOC fibers, varied considerably but averaged approximately 1 (Liberman and Brown, 1986). For guinea-pig fibers at frequencies near 1 kHz, both Q10s were higher, ~1.7 (Brown, 1989). For human MOC effects we found Q10s of approximately 2, 1-2 times sharper than the animal MOC Q10s. The sharper Q10s for human MOC fibers than for cat and guinea-pig MOC fibers is reminiscent of the results of Shera et al. (2002) who found that for SFOAEs and psychophysical measures, human auditory tuning was ~2 times sharper than the tuning in cats and guinea pigs in the frequency region near 1 kHz. Presuming that the functional role of MOC efferents is similar in humans, cats and guinea pigs, then one might expect that if cochlear tuning is sharper in humans compared to cats and guinea pigs, then human MOC tuning would also be sharper in cats and guinea pigs. Unfortunately, there are no similar OAE-based measurements of MOC tuning in cats and guinea pigs that would enable a better comparison of MOC tuning in humans versus animals.

Relationship of Our Results to Animal Physiology and the Underlying Anatomy

Although our data show relatively sharp tips to MOC tuning in humans, the data also show that tone and noise bursts at a moderate sound level (60 dB SPL) can produce significant |ΔSFOAEs| even when the elicitor sound is two, or more, octaves away from the probe frequency. A question of interest is the extent to which this wide spread of MOC effect originates centrally, peripherally or as a combination of both. Within the central nervous system (CNS) there may be convergence of excitation across frequency . TCs show that cat MOC fibers can be activated by high-level (70 or 90 dB SPL) tones bursts with frequencies as far as 2 octaves or more below the fiber's CF (Liberman, 1988, Fig. 8). In the periphery, each MOC fiber can innervate staggered and non-overlapping regions within the cochlea and may also exert indirect control on more remote OHCs through yet another neural network: the type II spiral ganglions that innervate both the MOC efferents as well as interconnecting OHCs with their reciprocal synapses (Thiers et al. 2002a, b). Hence, it is conceivable that MOC signals could spread away from the site of their endings in the organ of Corti so that efferent-effects need not exhibit the same narrow tuning as a single efferent fiber. Additional data are needed to resolve this issue.

Another issue of interest is the origin of the skew in MOC effect as a function of elicitor frequency relative to probe frequency. As above, it could come from the CNS or the cochlea. Anatomically, an *apical* offset of MOC projections in the cochlea has been observed in guinea pigs , i.e. the MOC-fiber BF was found to be higher than the characteristic frequency (CF) of the cochlear region it innervated (Brown, 2002). The offset found in our human study is in the opposite direction. Presuming that the inhibition produced by a MOC fiber is most effective for cochlear CFs near the region innervated by the MOC fiber, then the skew we have found (Figs. 4-6) implies that fibers that innervate the 1 kHz cochlear region have BFs of lower frequencies, i.e. a MOC fiber innervates a cochlear region more *basal* than its CF, on average. Since our MOC effect distribution was bimodal, perhaps some MOC fibers innervate regions basal to their BF and some innervate regions apical to their BF. We do not know if the different bias directions found in humans versus guinea pigs is due to a species difference, or some other factor. This question cannot be answered by obtaining labeled, BF-identified fibers in humans. In contrast, it should be possible to do comparable OAE experiments in animals, although it may require using awake animals.

Implications of the Results for the Role of MOC Efferents in Hearing

An offset between the frequency where MOC effects are measured and the most effective elicitor frequency is not expected from theories of hearing that postulate a frequency-specific MOC control of the cochlear amplifier, i.e. that each frequency region provides negative feedback to itself through MOC efferents (Guinan 1996). The |ΔSFOAE| offset such that elicitors at frequencies below the probe frequency are more effective, suggests that something more is happening. One possible reason for this offset is a MOC anti-masking role that alleviates the effects of upward spread of masking – the phenomenon that as masker level increases, masking grows more quickly at frequencies above the masker frequency than below the masker frequency. The upward spread of simultaneous masking may arise from a combination of excitation and suppression. Yasin and Plack (2005) found that suppression had a minimal effect on the slope of the masking function for masked mid-level signals (35-60 dB SPL), and that upward spread of masking was mainly produced by the compressive BM response to the signal in relation to the lower-frequency masker. Efferent activation can reduce the compressiveness of the BM response to mid-level stimulus (e.g. Dolan et. al., 1997; Cooper and Guinan, 2003) and increase the incremental discharge rate in response to an incremental increase in probe intensity - thereby improving the afferent output's signal-to-noise (Kawase et. al., 1993). That more potent elicitors of MOC effects were found for elicitors lower in frequency than the probe, regions - where the growth of masking with masker level is also known to be more rapid than a linear growth (upward spread of masking) - is consistent with the hypothesis of a feedback anti-masking role of medial efferents.

Acoustic trauma, that produces either temporary threshold shift (TTS) or permanent threshold shift (PTS), typically shows a half-octave offset, i.e. the region that is most damaged is one-half octave above the frequency of the traumatizing sound. It might be suggested that the typically half-octave offset of the most effective MOC elicitor frequency relative to the probe frequency is due to a MOC role in the prevention of acoustic trauma. This cannot be ruled out, but we think it is unlikely. The half-octave shift of acoustic trauma is caused by the cochlear region excited by a sound shifting basally as the sound increases in level (see Shera, 2001). Since this shifts the cochlear CF region and, presumably, MOC fibers in the same way, a MOC feedback effect to protect the cochlea would only need feedback to the site along the cochlea that was excited. Thus, the half-octave offset in |ΔSFOAE| that we have found would be unneeded. Perhaps more importantly, the MOC elicitors that we have used were at most 60 dB SPL, far from traumatizing levels. Furthermore, elicitors were most effective one half octave away from the probe frequency even for elicitor levels of 30 dB SPL.

Our result that for elicitors at frequencies above the probe frequency, NBN elicitors are more potent at eliciting |ΔSFOAEs| than tone elicitors is consistent with the hypothesis that sounds that provide more masking also elicit larger MOC feedback. Behavioral studies show that for maskers at frequencies above the frequency of the masked sound, NBN produces more masking than tonal maskers (Mott and Feth, 1986, Glasberg and Moore, 1994). But the masking effects of tone and NBN had also been documented to converge with longer signal durations (an increase from 10ms to 200 signal duration) because the signal threshold in noise decreased (Savel and Bacon, 2003). It is possible, perhaps likely, that the additional signal duration of 190 ms provided extra time for a masker-induced MOC response to increase and further decompress the BM input-output function thereby providing better signal detection. The extra signal duration is on the same time scale as the estimated MOC onset time constant in humans, approximately 150 to over 350 ms (Backus and Guinan, 2006).

V. Conclusion

In awake humans, MOC-effect OAE-based TCs near response threshold levels were found to be sharper than MOC efferent neural tuning in cats and guinea pigs. The TCs were V-shaped and had tips that were always displaced from the probe frequency and commonly towards lower frequencies. For mid-level elicitors (60 dB SPL), human MOC effects were less frequency selective and exhibited a skew in the |ΔSFOAE| response pattern such that elicitors at frequencies below the probe frequency were usually most effective at eliciting MOC activity. NBN elicited greater |ΔSFOAEs| than tone elicitors of the same SPL, especially for elicitor frequencies above the probe frequency resulting in |ΔSFOAE| curves with less skew and wider TCs with tips that could shift to higher frequencies than for tone MOC-effect TCs. The general heightened efferent activity in frequency regions below the probe is consistent with an anti-masking role for efferents in response to the upward-spread of masking.

VI. Appendix

Appendix A. |ΔSFOAE| and SFOAE Data Consistency Over Time

During preliminary studies, it was found that within a subject, MOC effects, quantified by |ΔSFOAEs|, taken months apart were repeatable and relatively consistent. Figure 10 shows examples taken from 2 subjects in whom data sets taken approximately 3-4 months apart showed no statistical difference (10 measurement repeats for each data set and subject) .

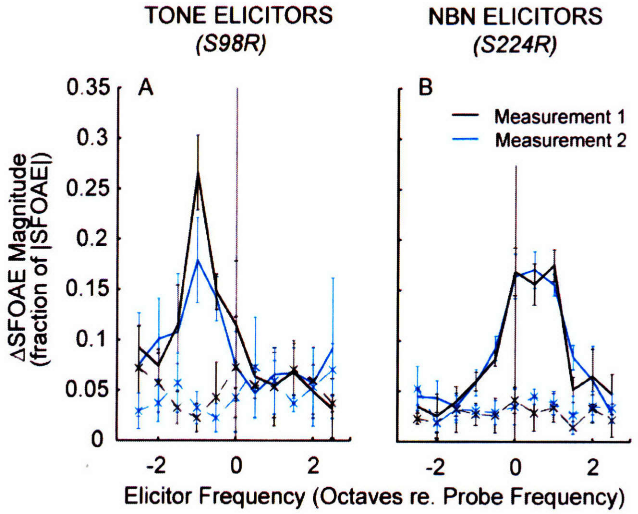

Figure 10: Comparison of |ΔSFOAE| measurements taken approximately 3-4 months apart in response to 60 dB SPL tone or half-octave noise bands centered at various frequencies in reference to the probe in 2 subjects. Each data set contains 10 stimulus repetitions. Error bars represent 1 standard error of the mean. Noise floor estimates (x) were obtained during a time interval when there was no |ΔSFOAE| (See Methods).

Another possible concern in terms of experimental design was whether or not significant error could be introduced by estimating SFOAE in a separate session from when |ΔSFOAEs| were measured. For example, if the variability in SFOAE over time were comparable or greater than that of |ΔSFOAE|, then normalization with SFOAE taken at a different point in time would likely not be representative of the SFOAE level corresponding to the |ΔSFOAE| measure resulting in gross inaccuracies. This issue was found to be negligible as the variability of SFOAE estimates were significantly less than |ΔSFOAE| measures such that on average the standard error of SFOAE measures were at least an order of magnitude less than the variability in |ΔSFOAE| measures across runs for a given subject. Details on the estimation of the propagation of error can be found in Appendix B.

The greater variance in the MOC effect (the |ΔSFOAE|), as compared to the variance of the SFOAE, could be due to the efferent system's dependence on input from the central nervous system which could add additional variability. Specifically, anatomical evidence of descending projections to MOC neurons suggest that MOC fibers may be activated, or the MOC response modulated, by descending input from higher centers that might produce attention effects on the MOC response. Since SFOAE exhibited a significantly smaller standard deviation than |ΔSFOAE| measures, we conclude that the variability seen in the |ΔSFOAE| contains negligible error propagated from the variability in SFOAE measures.

Appendix B. Propagation of Error

Estimation of the propagation of error can be quantified as follows (Bevington and Robinson, 2003). Suppose that the variable of interest, X, is a function of U and V

$$\mathrm{X} = \mathrm{f}(\mathrm{U},\mathrm{V},\ldots) \qquad \text{(eq. 9)}$$

If we knew the actual errors in each dimension ΔU and ΔV, we can estimate the error in X by expanding the estimated X, let's call it Xo, by expanding Xo about the point (U and V) in a Taylor Series. Looking only at the first terms in the Taylor expansion:

$$\mathrm{Xo} \approx \mathrm{X} + \Delta\mathrm{U}\left(\frac{\partial Xo}{\partial U}\right)_V + \Delta\mathrm{V}\left(\frac{\partial Xo}{\partial V}\right)_U \qquad \text{(eq. 10)}$$

If Δ corresponds to deviations from the mean, we can combine the expression above with the definition of the variance

$$\sigma_x^2 = \lim_{N\to\infty}\left[\frac{1}{N}\sum(X_i - \overline{X})^2\right] \qquad \text{(eq. 11)}$$

to get

$$\sigma_x^2 \cong \lim_{N\to\infty}\frac{1}{N}\sum\left\{(U_i - \overline{U})\left(\frac{\partial X}{\partial U}\right) + (V_i - \overline{V})\left(\frac{\partial X}{\partial V}\right) + \ldots\right\}^2 \qquad \text{(eq. 12)}$$

After expansion and defining the covariance between U and V as

$$\sigma_{UV}^2 = \lim_{N\to\infty}\left[\frac{1}{N}\sum(U_i - \overline{U})(V_i - \overline{V})\right], \qquad \text{(eq. 13)}$$

we get an approximation of σ_x^2 as

$$\sigma_x^2 \cong \sigma_U^2\left(\frac{\partial X}{\partial U}\right)^2 + \sigma_V^2\left(\frac{\partial X}{\partial V}\right)^2 + 2\sigma_{UV}^2\left(\frac{\partial X}{\partial U}\right)\left(\frac{\partial X}{\partial V}\right) \qquad \text{(eq. 14)}$$

If U and V are uncorrelated, the last term also drops to zero.

In our case, X, U and V would correspond to normalized |ΔSFOAE|, un-normalized |ΔSFOAE| estimates and SFOAE estimates respectively.

Appendix C. |ΔSFOAE| from contralateral, ipsilateral and bilateral elicitors using a 20 dB SPL probe tone in 1 subject.

Throughout the main text, elicitor frequency functions and TCs were obtained with the probe-tone level set to our standard 40 dB SPL. To see if using a 40 dB SPL probe influenced the results, in one subject, elicitor-level-and-frequency series were repeated with a 20 dB SPL probe tone. Figure 11 shows the tone-elicitor data using the 20 dB SPL probe as well as the TCs derived from them, and, for comparison, data from the same subject using the 40 dB SPL probe. The 20 dB SPL probe yielded data which had poorer SNRs than the 40 dB SPL probe and this exerted a considerable influence on the results. For instance, contralateral |ΔSFOAEs| with the 20 dB SPL probe did not pass the SNR criteria (see Methods) for the post-elicitor window so in Figure 11 contralateral |ΔSFOAEs| are shown only for the during-elicitor window.

One notable feature of the results from the 20 dB SPL probe tones is that the amplitudes of the |ΔSFOAEs| are higher than for 40 dB SPL probe tones. For the ipsilateral highest-level elicitors, the |ΔSFOAEs| were twice as large (Fig. 11: B versus E). However, at low elicitor levels, the |ΔSFOAE| appeared to be relatively lower, as if the threshold for eliciting a |ΔSFOAE| was higher. In many places it is difficult to be sure this is happening because of the poor SNR, but for bilateral tone elicitors, an increase in elicitor threshold seems clear (Fig. 11 A versus D).

The TCs from the 20 dB SPL probe tones are difficult to compare in detail to the TCs from 40 dB SPL probe tones because of the different SNRs. For the contralateral and ipsilateral elicitors, the 20 dB SPL frequency series did not pass the SNR criterion so the TCs derived from these had tips at the next highest level, 45 dB SPL. The Q10s from the 20-dB-SPL probes are wider than those from the 40-dB-SPL probes (Table 4), but this difference may be due to their poor SNR (as explained in the Discussion). For high level elicitors, the TCs from the 20-dB-SPL probes appear to be much wider 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 which also sets a higher criterion value for the rest of the TC. One interesting feature seen in the bilateral data is the shift of the TC tip frequency from below the probe frequency for the 40 dB SPL probe to above the probe frequency for the 20 dB SPL probe. This appears to be related to the large shift in elicitor threshold for elicitor frequencies below the probe frequency in the bilateral data (Fig. 11 Left).

In summary, at the 20 dB SPL compared to the 40 dB SPL probe level, there were larger normalized |ΔSFOAEs|, but the TCs were less accurate and did not show clear changes in tuning sharpness with probe levels. In one case, the frequency of the TC tip changed greatly, apparently because there was a change in the threshold for producing MOC effects for low-frequency elicitors.

	Bilateral, post-elicitor		Ipsilateral, post-elicitor		Contralateral, During-elicitor	
TT SPL:	20 dB	40 dB	20 dB	40 dB	20 dB	40 dB
Q_{10}:	2.5	3.1	2.2	2.6	1.3	2.3

Table 4: Q10 values from TCs for probe levels of 20 dB SPL and 40 dB SPL. Subject 181R. TCs shown in figure 11.

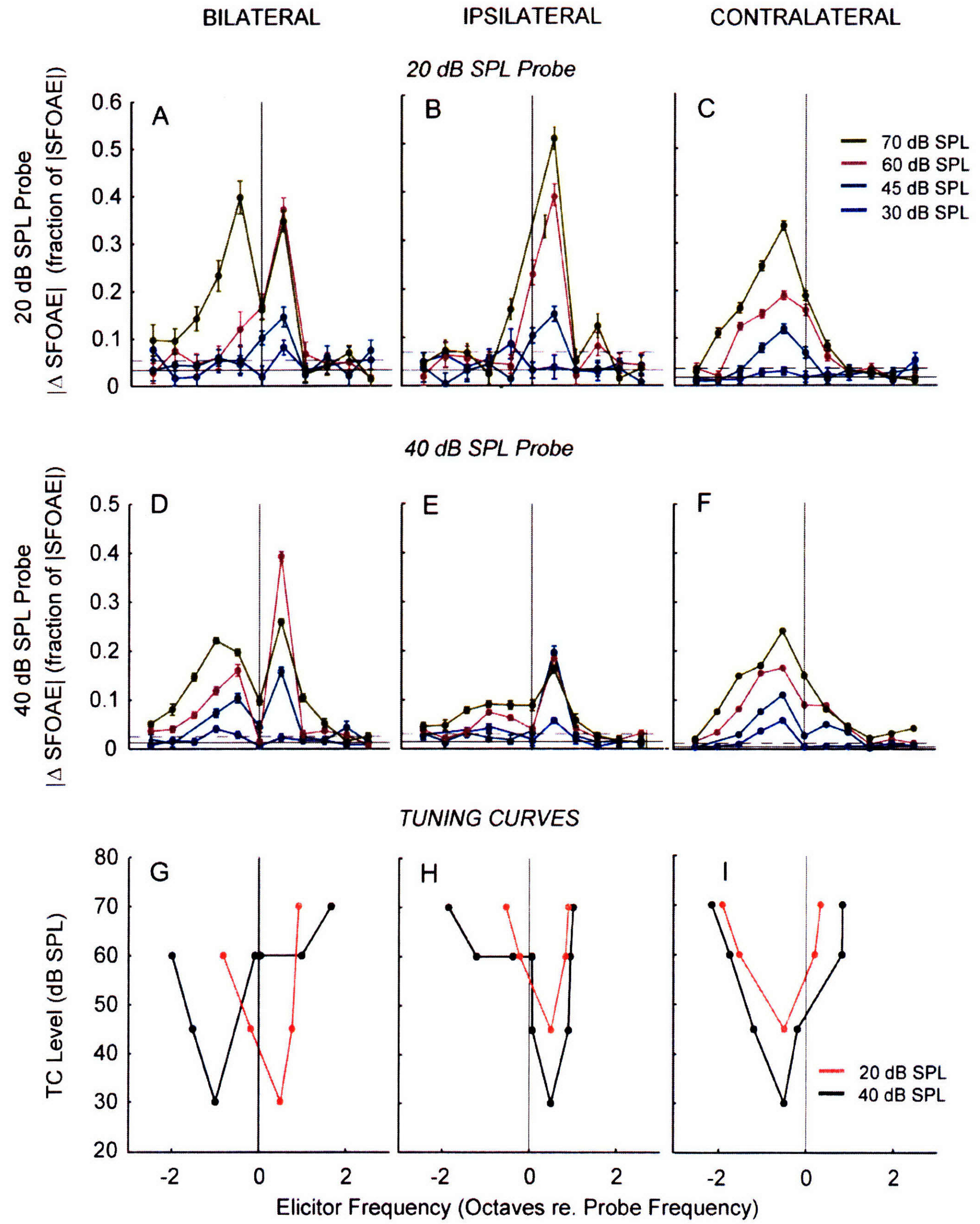

Figure 11. |ΔSFOAEs| from elicitor tone-frequency series at different sound levels and two probe intensity levels (top row = 20 dB SPL, middle row = 40 dB SPL) and the TCs (TCs) derived from them (bottom row). Error bars (A-F) are 1 standard error of the mean. The elicitors were: Bilateral (Column A), Ipsilateral (Column B), Contralateral (Column C) MOCR Level Series Q10 values are summarized in table 4.

Appendix D. Number of Required Bootstrap (Monte Carlo) Trials

Here we presented a brief derivation on the number of bootstrap realizations required to obtain a desired level of accuracy in the estimated probability for the hypothesis test statistic. A detailed explanation can be found elsewhere (Kay, 1998).

For a given statistic T, we want to estimate P=Pr{T>γ) as $\hat{P} \equiv {}^{M_\gamma}\!/_{M}$, where M is the total number of realizations and M_γ is the number of trials for which T > γ. To determine the required M for a satisfactory estimate of $\hat{P}$, we must first determine $\hat{P}$'s probability distribution function (PDF). A natural estimator for P can be defined as follows:

$$\hat{P} = \frac{1}{M}\left(\sum_{i=1}^{M} \xi_i\right), \qquad \text{(eq. 15)}$$

where ξ_i are independent and identical (i.i.d.) Bernoulli random variables such that

$$\xi_i = \begin{matrix} 1 \text{ if } \mathrm{Ti} > \gamma \\ 0 \text{ if } \mathrm{Ti} < \gamma \end{matrix} \qquad \text{(eq. 16)}$$

Invoking the central limit theorem allows $\hat{P}$ to be approximated by a Gaussian distribution for large M so that the mean

$$\mathrm{E}(\hat{P}) = \frac{1}{M}\sum_{i=1}^{M} E(\xi_i) = \frac{1}{M}\sum_{i=1}^{M} 1 \bullet \Pr\{T_i \succ \gamma\} = \mathrm{P} \qquad \text{(eq. 17)}$$

And the variance

$$\mathrm{Var}(\hat{P}) = \frac{Var(\xi_i)}{M} = \frac{P(1-P)}{M} \qquad \text{(eq. 18)}$$

So we have

$$\hat{P} \to \mathrm{N}\left(P, \frac{P(1-P)}{M}\right) \qquad \text{(eq. 19)}$$

Then the relative error can be defined as

$$e = \frac{\hat{P} - P}{P} \to N\left(0, \frac{1-P}{MP}\right) \qquad \text{(eq. 20)}$$

If we want to make sure that e does not exceed some predefined limit ε in absolute value for 100(1-α)% of the time, we need

$$\Pr\{|e| \succ \varepsilon\} \le \alpha \text{, or} \qquad \text{(eq. 21)}$$

$$2\Pr\{e \succ \varepsilon\} \leq \alpha \tag{eq. 22}$$

Resulting in

$$2Q\left(\frac{\varepsilon}{\sqrt{\frac{1-P}{MP}}}\right) \leq \alpha, \tag{eq. 23}$$

where Q is the cumulative distribution function of *e*[8].

Solving for M gives

$$M \geq \frac{\left[Q^{-1}\left(\alpha/2\right)\right]^2}{\varepsilon^2 P}(1-P) \tag{eq. 24}$$

Where $Q^{-1}\left(\alpha/2\right)^2$ is the inverse cumulative distribution function[9] of *e*.

So in summary, suppose we predefined an allowable relative absolute error,

$$e = \frac{\left|\hat{P} - P\right|}{P}, \tag{eq. 25}$$

where P is the probability being estimated.
Then, if we want to make sure that *e* does not exceed a predefined limit ε in absolute value for 100(1-α)% of the time, we need M (the number of realizations) to satisfy

$$M \geq \frac{\left[Q^{-1}\left(\alpha/2\right)\right]^2}{\varepsilon^2 P}(1-P), \tag{eq. 26}$$

---

[8] The cumulative distribution function (CDF) of a probability distribution, *f(u)*, evaluated at some number x, is the probability that the distribution is less than or equal to x. Hence for a normal distribution with mean μ and standard deviation σ, the CDF is

$$Q_{\mu,\sigma^2}(x) = \int_{-\infty}^{x} f_{\mu,\sigma^2}(u)du = \frac{1}{\sigma\sqrt{2\pi}}\int \exp\left(-\frac{(u-\mu)^2}{2\sigma^2}\right)du = Q\left(\frac{x-\mu}{\sigma}\right) \tag{eq. 27}$$

[9] In general, it can be shown that for a normal cumulative distribution function with mean μ and standard deviation σ, the inverse cumulative distribution function can be expressed as

$$Q^{-1}_{\mu,\sigma^2}(p) = \mu + \sigma Q^{-1}_{0,1}(p) = \mu + \sigma\sqrt{2}erf^{-1}(2p-1), p \in (0,1) \tag{eq. 28}$$

Where erf() is a special function called the error function and is defined as

$$erf(y) = \frac{2}{\sqrt{\pi}}\int_0^y e^{-t^2}dt \tag{eq. 29}$$

where Q is the cumulative distribution of e and ε is the predefined limit in absolute error on e (Kay, 1998). In other words, with M trials, we can achieve a $\hat{P}$ estimate that is accurate within ε of the true proportion at a 100(1-α)% confidence level. In this study, we arbitrarily set $\varepsilon = 0.01$. To obtain that error level for 95% of the time (α=0.05) for P=0.05, $M \geq 3719$ would suffice. For all bootstrapping analysis, we set M arbitrarily at 4000 which exceeds the minimum M estimate.

VII. References

Backus, B.C. (2007). 'Bias due to noise in otoacoustic emission measurements,' J Acoust Soc Am 121(3):1588-1603.

Backus, B.C. and Guinan, J. J. Jr.. (2006). 'Time-course of the human medial olivocochlear reflex,' J. Acoust. Soc. Am. 119(5 Pt 1): 2889-904.

Backus, B.C. and Guinan, J.J. Jr. (2007). 'Measurement of the distribution of Medial olivocochlear acoustic reflex strengths across normal hearing individuals via otoacoustic emissions,' J. Assoc Res. Otolaryngol. 8(4): 484-496.

Bevington, P.R., and Robinson, D.K. (2003). 'Error Analysis' in Data Reduction and error Analysis, edited by Bruflodt, D. and Cotkin, J.C. (McGraw-Hill, New York, NY) pp. 36-49.

Brown, M.C. (1989). 'Morphology and response properties of single olivocochlear fibers in the guinea pig,' Hear Res. 40(1-2):93-109.

Brown, M.C. (2002). 'Cochlear projections of single medial olivocochlear fibers in the guinea pig,' Assoc. Res. Otolaryngol. Abstr. 25:#310.

Chery-Croze, A., Moulin, A., Collet, L. (1993). 'Effect of contralateral sound stimulation on the distortion product 2f1-f2 in humans: Evidence of a frequency specificity,' Hear Res 68: 53-58.

Cooper, N.P. and Guinan, J.J. Jr. (2003). 'Separate mechanical processes underlie fast and slow effects of medial olivocochlear efferent activity,' J. Physiol. 548(Pt 1): 307-312.

Dallos, P. 1992. The active cochlea. J. Neurosci. 12, 4575-4585.

Dolan, D.F., Guo, M.H., Nuttall, A.L. (1997). 'Frequency-dependent enhancement of basilar-membrane velocity during olivocochlear bundle stimulation,' J. Acoust. Soc. Am. 102:3587-3596.

Efron, B. and Tibshirani, R. J. (2000). 'An introduction to the bootstrap,' edited by Bradley Efron and Robert Tibshirani. (CRC Press LLC).

Glasberg, B. R. and Moore, B. C. J. (1994). 'Growth-of-masking functions for several types of maskers,' J. Acoust. Soc. Am. 96, 134-144.

Guinan, J. J., Jr. (1990). "Changes in stimulus frequency otoacoustic emissions produced by two-tone suppression and efferent stimulation in cats," in *Mechanics and Biophysics of Hearing*, edited by P. Dallos, C. D. Geisler, J. W. Matthews, and C. R. Steele (Springer Verlag, Madison, Wisconsin), pp. 170-177.

Guinan, J.J., Jr. 1996. The Physiology of Olivocochlear Efferents. In: Dallos, P.J., Popper, A.N., Fay, R.R., (Eds.), The Cochlea. Springer-Verlag, New York. pp. 435-502.

Guinan, J.J.Jr., Backus, B., Lilaonitkul, W, Aharonson, V. (2003). 'Medial olivocochlear efferent reflex in humans: otoacoustic emission (OAE) measurement issues and the advantage of stimulus frequency OAEs, J Assoc Res Otolaryngol 4(4):521-540.

Kawase, T., Delgutte, B., Liberman, M.C. (1993). 'Anti-masking effects of the olivocochlear reflex, II: Enhancement of auditory-nerve response to masked tones,' J. Neurophysiol. 70: 2533-2549.

Kay, S.M. (1998). 'Summary of important PDFs', in Fundamentals of Statistical Signal Processing Volume II: Detection Theory, edited by Little, C. and Goodwin, B. (Prentice-Hall, Upper Saddle River, NJ) pp. 20-59.

Liberman, M.C.. (1988). 'Response properties of cochlear efferent neurons: monaural vs. bilateral stimulation and the effects of noise,' J Neurophysiol 60:1779-1798.

Liberman, M.C., Brown, M.C. (1986). 'Physiology and anatomy of single olivocochlear neurons in cat,' Hear Res, 24:17-36

Maison, S., Micheyl, C., Andeol, G., Gallego, S., Collet, L. (2000). 'Activation of olivocochlear efferent system in humans: influence of stimulus bandwidth,' Hear Res 140:111-125.

Mott, J.B. and Feth, L.L. (1986). 'Effects of the temporal properties of a masker upon simultaneous masking patterns,' in Auditory Frequency Selectivity, edited by B. C. J. Moore and R. D. Patterson (Plenum, New York), pp. 381-386.

Mountain, D.C. 1980. Changes in endolymphatic potential and crossed olivocochlear bundle stimulation alter cochlear mechanics. Science 210, 71-72.

Norman, M., Thornton, A.R.D. (1993). 'Frequency analysis of the contralateral suppression of evoked otoacoustic emissions by narrow-band noise,' Br J Audiol 27:281-289.

Savel, S. and Bacon, S.P. (2003). 'Effectiveness of narrow-band versus tonal off-frequency maskers,' J. Acoust. Soc. Am. 114(1): 380-385.

Shera, C.A. (2001). 'Intensity-invariance of the fine time structure in basilar-membrane click responses: implications for cochlear mechanics,' J. Acoust. Soc. Am. 110(1):332-348.

Shera, C.A., Guinan, J.J., Jr. Oxenham, A.J. (2002). 'Revised estimates of human cochlear tuning from otoacoustic and behavioral measurements,' Proc Natl Acad Sci U S A, 99: 3318-3323.

Siegel, J.H., Kim, D.O. 1982. Efferent neural control of cochlear mechanics? Olivocochlear bundle stimulation affects cochlear biomechanical nonlinearity. Hearing Res. 6, 171-182.

Thiers, F. A., Burgess, B. G., and Nadol, J.B., Jr. (2002a). 'Axodendritic and dendrodendritic synapses within outer spiral bundles in a human,' Hear. Res. 164:97-104.

Thiers, F.A., Burgess, B.J., and Nadol, J.B. (2002b). 'Reciprocal innervation of outer hair cells in a human infant,' J Assoc Res otolaryngol, 3:269-278.

Van Dijk, P. and H. P. Wit (1988). 'Phase-lock of spontaneous otoacoustic emissions to a cubic difference tone. Basic Issues in hearing. H.P.W.H.H. Duihui. London, London Academic:101-105.

Veuillet, E., Collet, L., Duclaux, R. (1991). 'Effect of contralateral acoustic stimulation on active cochlear micromechanical properties in human subjects: Dependence on stimulus variables,' J Neurophysiol, 65:742-735.

Yasin, I., Plack, C.J. (2005). 'The role of suppression in the upward spread of masking,' J. Assoc. Res. Otolaryngol. 6(4): 368-77.

Chapter 3: The Frequency Dependences of the Contralateral, Ipsilateral and Bilateral Medial-Olivocochlear-Efferent Acoustic Reflexes in Humans as Functions of Probe Frequency

Abstract

This study investigated the frequency selectivity of human medial olivocochlear (MOC) effects for three different probe-frequency regions, 0.5, 1 and 4 kHz. MOC effects were elicited by 60 dB SPL contralateral, ipsilateral and bilateral tones or half-octave noise-bands (NBNs) centered at various frequencies relative to the probe frequency. The response metric was the MOC-induced change in the stimulus frequency otoacoustic emission (SFOAE) from a 40 dB SPL probe tone. The analysis of the MOC effect was done in two ways, ΔSFOAE and SFOAEMOC. The overall change in the SFOAE produced by MOC stimulation, ΔSFOAE, varied with probe frequency, elicitor laterality, elicitor frequency and elicitor bandwidth. Significant ΔSFOAE magnitudes (|ΔSFOAE|) were seen for a wide range of elicitor frequencies, e.g. for elicitor frequencies at least 1½ octaves away from the probe frequency for all probe frequencies. |ΔSFOAE|s were sometimes skewed so that elicitors at frequencies above (for the 0.5 kHz probe) or below (for the 1 kHz probe) the probe frequency were most effective. The largest |ΔSFOAE|s were for 0.5 kHz probes and the smallest for 4 kHz probes, opposite the pattern of MOC innervation in humans and cats, which indicates that the strength of the MOC acoustic reflex is controlled more by central factors than peripheral innervation. When MOC effect was looked at as SFOAEMOC, the MOC-inhibited SFOAE relative to the original SFOAE, surprisingly, the SFOAEMOC magnitude decreased and phase changes appeared to be separate functions of elicitor frequency. The MOC inhibition of the SFOAEMOC magnitude was largest for elicitor frequencies near the probe frequency, whereas the MOC-induced change in SFOAEMOC phase was largest for elicitor frequencies remote from the probe frequency. One hypothesis is that elicitor-frequencies near the probe frequency predominately reduce the traveling wave from the probe-tone, whereas elicitor-frequencies more remote from the probe frequency shift the traveling wave along the basilar membrane by selectively inhibiting apical or basal parts of the traveling-wave envelope.

Abbreviations

AN	Auditory Nerve	**OAE**	Otoacoustic Emission
BF	Best Frequency	**SFOAE**	Stimulus Frequency Otoacoustic Emission
CF	Characteristic Frequency	**$\text{SFOAE}_{\text{MOC}}$**	Remaining SFOAE from MOC-inhibition
DPOAE	Distortion-Product Otoacoustic Emission	**ΔSFOAE**	MOC-Induced Change in SFOAE
MEM	Middle-Ear Muscle	**SNR**	Signal-to-Noise Ratio
MOC	Medial Olivocochlear	**TC**	Tuning Curve
NBN	Half-Octave Narrow-Band Noise	**TEOAE**	Transient-Evoked Otoacoustic Emission

I. Introduction

The medial olivocochlear (MOC) efferents are part of a system that can alter the gain of cochlear biomechanics, such that when activated, the MOC acoustic reflex reduces the outer hair cells' contribution to the cochlear amplifier and thereby basilar membrane motion is reduced. Data from animals indicate that the organization and physiology of medial efferents vary along the length of the cochlea. For example: (1) Cat MOC innervation density varies along the length of the cochlea and is largest slightly basal of the center of the cochlea (Guinan et al., 1984). (2) Cat MOC fiber responses to monaural tones vary with fiber best frequency (BF) such that fibers with BFs below 10 kHz tended to have lower thresholds, higher discharge rates and shorter latencies (Liberman, 1988). (3) MOC tuning curves in cats and guinea pigs are shaper at higher BFs (Liberman and Brown, 1986; Brown, 1989). (4) In guinea pig, the maximum rates of MOC fibers increases with BF (Brown et al. 1998). With ample evidence in other species of anatomical and physiological differences along the cochlear length, it is of interest to explore human MOC effects at different cochlear frequency regions. The purpose of this study is to extend our measurement of the frequency selectivity of MOC effects with probe frequencies higher and lower than the 1 kHz region probed in chapter 2. Of additional interest is to analyze the resulting MOC-induced changes in both the magnitude and phase of the SFOAE. Such information may provide insights on the mechanism of MOC coupling to cochlear mechanics.

In human studies, MOC effects are commonly quantified as the elicitor-induced change in the magnitude of the otoacoustic emission (OAE) of choice, but most OAEs have significant drawbacks as efferent probes (Guinan et al., 2003). Stimulus frequency otoacoustic emissions (SFOAEs) - soft cochlear "echoes" generated at the same frequency as the tone stimulus – have been used because they minimize many of these drawbacks (Guinan et al., 2003; Backus and Guinan, 2006, 2007). In addition to the SFOAE's appeal as the most frequency selective probe, the low-level tone stimuli used to generate SFOAEs are only weak elicitors of MOC effects at the probe frequency, so measurements with SFOAEs appear to be the least disturbed by MOC activity elicited by the probe sound (Guinan et al., 2003).

Another important advantage of SFOAEs as probes of MOC effect is that there is a well-developed theory that explains their production, so that measurements of MOC effects on SFOAEs may lend themselves to interpretation in terms of the underlying changes in cochlear mechanisms more readily than other OAEs. The *theory of coherent reflection filtering* for SFOAE generation (Shera and Zweig, 1993b; Zweig and Shera, 1995) models SFOAEs as the sum of coherent back-scattered wavelets from densely and randomly distributed cochlear impedance perturbations (e.g. spatial variations in outer-hair-cell (OHC) number, geometry and efficacy) near the region of the basilar membrane (BM) traveling wave (TW) peak. At low levels, the BM transfer function (the frequency-domain analog of the time-domain BM traveling wave) manifests many characteristics of minimum-phase filters including the reciprocal relation between the filter bandwidth and phase slope (Zweig, 1976). As a consequence, the theory predicts that changes in the shape of the TW, for example from altering the gain of the cochlear amplifier, will give rise to predictable changes in SFOAE phase. This theory indicates that in addition to MOC-induced changes in SFOAE amplitude, changes in SFOAE phase are also important for giving insight into the underlying changes in cochlear mechanics. In all previous work that explored MOC effects on OAEs, changes in phase have been ignored. In contrast, one focal point of this chapter will be to look at both the magnitude and phase changes produced by MOC activity.

In this Chapter, the frequency tuning of MOC effects at a low (~0.5 kHz) and a high (~4 kHz) probe frequency are presented. These data, together with the 1 kHz data of chapter 2, give a picture of how MOC tuning changes as a function of location along the cochlea. As in chapter 2, the elicitors of MOC activity are mid-level (60 dB SPL) pure tones, or half-octave narrow-band noises (NBNs), presented contralaterally, ipsilaterally or bilaterally, over a wide range of frequencies relative to the probe frequency. MOC effects were measured by the changes in SFOAEs from 40 dB SPL tones. We analyzed the MOC-induced changes in two ways: (1) by the change in the SFOAE, ΔSFOAE, as in chapter 2, and (2) by the amplitude and phase of the MOC-inhibited SFOAE, $SFOAE_{MOC}$, relative to the uninhibited SFOAE. The second method provides the most useful phase measure. The data show patterns of MOC effects that are different for the different probe regions and elicitor lateralities. More surprisingly, the MOC-induced changes in the magnitude and phase of the SFOAE do not co-vary but appear to be separate functions of elicitor frequency. There appears to be different efferent effects on cochlear biomechanics when induced by elicitor frequencies near the probe frequency versus elicitor frequencies remote from the probe frequency.

II. Methods and Analysis

A. Subjects

All subjects included in this study had clinically normal hearing thresholds in both ears (within 20 dB re. ANSI pure tone threshold from 250 Hz to 4 kHz). Measurements were conducted in a sound-proof room. A warning light was automatically turned on before each stimulus presentation and the subject was instructed to sit still during the time that the light was on and sounds were presented. For each probe frequency, the same subjects were used for tone and NBN elicitor experiments. Subjects were rejected from the study if (1) the subject's middle-ear muscle (MEM) contractions were significant at the stimulus levels used for the experiments (See MEM-test in section D), (2) the subject was unable to remain awake and sit still during the experiment, or (3) the subject did not return to complete the study. A minimum SNR criterion was set such that data sets from any given ear and elicitor laterality were rejected from the study if the SFOAE amplitude or the maximum MOC effect within an elicitor frequency series had an SNR < 3 (~9.5 dB). This minimum SNR criterion was set to avoid significant amplitude estimation biases resulting from low SNR (Backus, 2007). The 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. The number of ears and subjects involved in this study are summarized in table 1.

Probe Frequency Region	Subjects Included / Subjects Tested		Number of Ears included in Study	Subject Age Range (Years)	Average Subject Age (Years)
	Male	Female			
0.5 kHz	1/3	4/5	8	22-31	24.4
1.0 kHz	3/4	4/4	11	22-33	27.5
4.0 kHz	0/5	3/7	3	22-40	28

Table 1: Summary of subject gender, subject age and the number of subjects included in the study.

B. Acoustic Stimuli

As a probe sound to evoke SFOAEs in both ears, a 40-dB SPL continuous tone[10] selected at a frequency within ±10% of 0.5, 1 or 4 kHz was presented bilaterally through the earphones of 2 Etymotic ER10C

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[10] Contralateral tones at the probe frequency presented at 40 dB SPL were found to be weak elicitors of efferent response (Guinan et al., 2003).

acoustic assemblies. For each subject, a probe frequency was selected that: (1) was at least 100 Hz away from any spontaneous OAE with magnitude above -10 dB SPL (this was done to avoid possible entrainment – van Dijk, et al., 1988), and (2) produced the largest ΔSFOAE magnitude to a 60 dB SPL, contralateral broad-band noise (so that the signal/noise ratio (SNR) criteria could be reached with the smallest number of stimulus repeats).

To elicit MOC activity, a 60 dB SPL tone or half-octave NBN was presented ipsilaterally, contralaterally or bilaterally for 2.5 s. Preceding the elicitor was a 0.5 s onset period from which the baseline response was measured, and following the elicitor was a 2 s period for recovery. The resulting stimulus repetition period was 5 s (Fig. 1A). 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 NBN elicitor. Elicitors were presented in half-octave steps, and were presented in a randomized order to avoid bias. Elicitor frequencies were between 2 octaves below and 3 octaves above the 0.5 kHz probe, 2.5 octaves below and 2.5 octaves above the 1 kHz probe, 3.5 octaves below and 1 octave above the 4 kHz probe. Data gathering runs of tone or NBN elicitor frequency series were interleaved to minimize possible long-term variation in subject responses and allow direct comparison of the results.

The baseline SFOAE (the SFOAE preceding the MOC elicitor) was measured from the vectorial difference of the ear-canal sound pressure from the 40 dB SPL probe tone with and without a 60 dB SPL suppressor tone at 110 Hz below the probe frequency[11]. The baseline SFOAE vector was measured separately from the induced-change in SFOAE in runs in which the suppressor was presented for 0.5 s every 1 s (Fig. 1B). For both suppressor-tones and MOC-elicitors, 5-ms rise/fall cosine ramps were introduced at the presentation edges to minimize spectral splatter. Consecutive elicitor or suppressor presentations had opposite polarities so that upon averaging, their acoustic waveforms would cancel leaving a residual measure equal to the amount of induced change in the SFOAE vector.

Calibrations of the acoustic output from the two sound sources in each ER10C acoustic assembly were done (using the microphone in the ER10C) at the beginning of every data gathering session and frequently within a session. Noise bursts were made to be spectrally flat by applying these calibrations.

C. Measurement Analysis

Responses were rejected as being contaminated with artifacts when the difference between one pair of responses and the next pair exceeded a criterion. Stimulus pairs were used because elicitors (or suppressors) were alternated in polarity across stimulus repetitions. Multiple response pairs were vectorially averaged to achieve response averages with $N \geq 50$ stimulus repetitions. The averaged waveforms were then heterodyned to obtain the complex waveform of the response at the probe frequency. Details of the heterodyning method and specification of the frequency domain filtering can be found elsewhere (Guinan et al, 2003).

The complex amplitude of the ear canal sound pressure at the probe frequency, P(t), is the sum of the probe-tone and the evoked SFOAE(t) complex amplitude. An MOC elicitor, or a suppressor, can induce a change in the SFOAE and thereby change P(t). Changes in the SFOAE(t), ΔSFOAE(t), were calculated from P(t) by the vectorial difference between P(t) and $P_{baseline}$ where $P_{baseline}$ is the vector average of P(t) between 50-450 ms, i.e. the average P(t) before the onset of the suppressor or MOC elicitor (see Guinan

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[11] Backus and Guinan (2007) found that the SFOAE obtained using these parameter values can underestimate the true SFOAE amplitude, i.e. the suppressor produces only 80-100% suppression. The variability in the *degree* of underestimation could have increased the standard error of our group averages. However, underestimation of the SFOAE magnitude did not affect the shape of the MOC effect curves because, for a given ear, all points were normalized by the same SFOAE measure.

2003 for more detail). The MOC-induced change was then expressed as a fraction of the SFOAE by dividing ΔSFOAE(t) by the baseline SFOAE vector. That is,

$$\Delta\text{SFOAEn}(t) = \frac{P(t) - P_{\text{Baseline}}}{\text{SFOAE}} = \frac{\Delta\text{SFOAE}}{\text{SFOAE}} \qquad \text{(eq. 1)}$$

Where,

$P(t)$ = the complex heterodyned measurement, and $0 < t < 5\text{s}$.

P_{Baseline} = the vectorial average of $P(t)$, and $0.05 < t < 0.45\text{s}$

SFOAE = the complex baseline stimulus frequency otoacoustic emission evoked by the probe tone.

ΔSFOAEn(t) = the change in the SFOAE normalized by the baseline SFOAE.

In the equation above, SFOAE(t) and ΔSFOAE(t) were the raw, un-normalized values and ΔSFOAEn(t) was the normalized value. In all of the remaining, we will use only the normalized values and will drop the "n" so that henceforth ΔSFOAE(t) = ΔSFOAEn(t) of above.

Normalized ΔSFOAE(t) data were vectorially averaged in either a 0.4 s "during-elicitor" time window ending 0.05 s before the end of the elicitor (for contralateral ΔSFOAE(t)), or a 0.1 s "post-elicitor" time window starting at 0.05 s after the end of the elicitor (for ipsilateral and bilateral Δ SFOAE(t) and, for comparison, contralateral ΔSFOAE(t)). Averaging in the post-elicitor window avoids two-tone-suppression effects of the probe that can be evoked by ipsilateral and bilateral elicitors, but at the expense of capturing the MOC effect during its decay. Two-tone-suppression is absent for contralateral elicitors so the contralateral ΔSFOAE(t) can be averaged from a during-elicitor window near the end of the elicitor presentation which allows us to capture the maximum MOC effect elicited. The noise floor estimate was obtained from averaging the ΔSFOAE(t) in a time-window of the same duration as the (during or post-elicitor) data-analysis time window, but positioned such that the end of the noise time window was 50 ms before the end of a stimulus repetition period.

The change in the SFOAE produced by MOC activity was considered in two ways. The first way, ΔSFOAE, was explained above, and is shown in Figure 2 for a fixed time point (or for the average in a response time window). The second way is as the SFOAE obtained during MOC inhibition, $\text{SFOAE}_{\text{MOC}}$, also shown in Figure 2. With the two measured quantities being the SFOAE and the ΔSFOAE vectors, $\text{SFOAE}_{\text{MOC}}$ was calculated as:

$$\text{SFOAE}_{\text{MOC}} = \frac{\text{SFOAE} - \Delta\text{SFOAE}}{\text{SFOAE}} = \frac{A_{\text{SFOAE}_{\text{MOC}}} e^{i\theta_{\text{SFOAE}_{\text{MOC}}}}}{A_{\text{SFOAE}} e^{i\theta_{\text{SFOAE}}}} = \frac{A_{\text{SFOAE}_{\text{MOC}}}}{A_{\text{SFOAE}}} e^{i(\theta_{\text{SFOAE}_{\text{MOC}}} - \theta_{\text{SFOAE}})} \qquad \text{(eq. 2)}$$

In eq. 2 above, ΔSFOAE is the value of ΔSFOAE before it was normalized by the SFOAE magnitude (throughout the rest of the text, ΔSFOAE refers to the normalized ΔSFOAE). This equation for $\text{SFOAE}_{\text{MOC}}$ includes normalizing by the magnitude of the original SFOAE magnitude, and referencing the phase of $\text{SFOAE}_{\text{MOC}}$ to the phase of the original SFOAE.

D. Middle-ear-muscle (MEM) contraction test

A MEM test was performed on each subject to ensure that the MEMs were not activated at the stimulus levels used. In this test, a 65 dB SPL continuous suppressor tone at 110 Hz above the probe frequency was presented in addition to the normal acoustic stimuli. With this paradigm, only MEM contractions produce a change in the sound pressure at the SFOAE probe frequency. Thus, 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 has been no significant MEM contraction. Details of the experimental rational can be found in the Methods section of Chapter 2.

E. Determining the statistical significance of variations across parameters

To determine the statistical significance of the variations of ΔSFOAE magnitude 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 data passed the Lillifores test for normality. If they did not pass, the Friedman non-parametric two-way ANOVA was used. Statistical significance was accepted at the 0.05 level. The data were compared to a control data set that measured the response under the Null-hypothesis of no MOC effect. The control data were the noise floor measurements taken from a time-window of the same duration as the (during or post-elicitor) data-analysis time window, but positioned such that the end of the noise time window was 0.05 s before the end of a stimulus repetition period.

ANOVA to test the significance of ΔSFOAE magnitude variations across elicitor frequency included data from the whole elicitor frequency range. On the other hand, ANOVA to determine the significance of ΔSFOAE magnitude variation across subject, ear and laterality were carried out using ΔSFOAE magnitudes to elicitor frequencies within a restricted frequency range of: -2 to 2 octaves re. the 0.5 kHz probe, -0.5 to 2.5 octaves re. the 1 kHz probe, and -1 to 1 octaves re. the 4 kHz probe. The frequency-range restriction was done to avoid using ΔSFOAE magnitudes that were too close to the noise floor. This was particularly important for the 4 kHz probe.

F. Testing the hypothesis of ΔSFOAE magnitude asymmetry along the elicitor frequency axis

For a data set consisting of ΔSFOAE magnitude as a function of elicitor center frequency from different subject ears at a single probe-frequency region, we wanted to determine whether the pattern of effects was asymmetric in elicitor frequency relative to the probe frequency. That is, we wanted to know if the ΔSFOAE magnitudes from elicitor frequencies below the probe frequency were different than those from above the probe frequency to a statistically significant degree. To determine if the ΔSFOAE-magnitude frequency response curve averaged across subjects was statistically asymmetric, we determined the sampling distribution for the skewness statistic, b_1, under the Null hypothesis that the distribution was symmetric about the probe frequency. We used a bootstrap with replacement method explained in detail in the methods section (section E2) of Chapter 2.

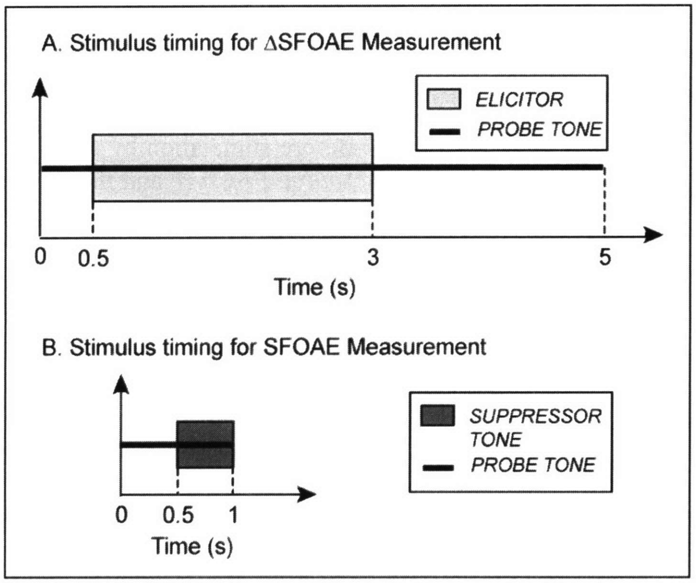

Figure 1. Temporal presentation of stimuli. **A**. For the measurement of the elicitor-induced ΔSFOAE, there was an initial delay of 0.5 s to establish the baseline response, then a 2.5 s tone or noise burst to elicit MOC activity, followed by a 2 s recovery period. This stimulus pattern was repeated every 5 s with the polarity of the elicitor alternated so that upon averaging the measurements, the elicitors would cancel leaving a residual pressure equal to elicitor-induced ΔSFOAE. **B**. For the SFOAE measurement, there was an initial delay of 0.5 s to establish the baseline response, then a 0.5 s suppressor tone at 110 Hz below the probe frequency. This stimulus pattern was repeated every 1 s with the polarity of the suppressor alternated.

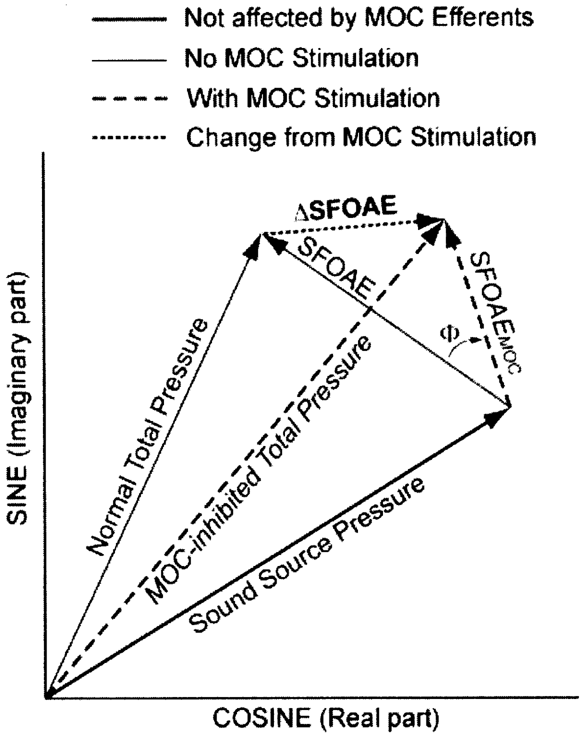

Figure 2. Vector diagram of MOC-elicitor effects on sound pressures in the ear canal. The arrows are vectors in the complex plane such that the length of the arrow represents the magnitude and the direction of the arrow represents the phase. Before stimulation by the MOC-elicitor, the *Sound Source Pressure* and the SFOAE summate to form the *Normal Total Pressure* in the ear canal. In the presence of an MOC-elicitor the SFOAE magnitude and phase are changed as shown by SFOAEMOC resulting in a new ear-canal sound pressure (*MOC-inhibited Total Pressure*). The change in the ear canal pressure shows the resulting change in the SFOAE, ΔSFOAE. Note that the angle ϕ shows the phase delay of SFOAEMOC from the SFOAE phase, opposite the sign convention used in the other figures.

III. Results

MOC effects were quantified near 0.5 kHz, 1 kHz and 4 kHz using both tone and NBN elicitors that were swept in frequency over as wide a range as practical above and below the probe frequency. Figure 3 shows examples from one subject of typical ΔSFOAE magnitudes for NBN elicitors and three probe frequencies, as well as the corresponding MEM-test results, all as functions of elicitor frequency. Note that the ΔSFOAE magnitudes were above the noise level for many of the elicitor frequencies, but the values from all of the MEM-test runs are close to, or less than, the mean noise level. For all of the stimulus frequencies and levels used in this study, MEM tests were done and showed no evidence of MEM contractions.

MOC effects were analyzed in two ways: (1) as the magnitude of the elicitor-induced change in the SFOAE (|ΔSFOAE|) and 2) the MOC-inhibited SFOAE vector, $SFOAE_{MOC}$ (Fig. 2). Both were normalized so that they are expressed as a fraction of the original SFOAE (see Methods). The $SFOAE_{MOC}$ metric has the advantage of showing magnitude and phase changes that can be most readily interpreted in terms of underlying changes in cochlear mechanics. The ΔSFOAE magnitude has the advantage of capturing both magnitude and phase changes of $SFOAE_{MOC}$ in one quantity, and typically has a better SNR than the magnitude and phase changes of $SFOAE_{MOC}$. By either metric, the difference between the average left and right ear MOC effects was not significant at any probe frequency [12], so further analysis was done with the data from both ears combined. For all probe frequencies, significant inter-subject variation was observed in the ΔSFOAE magnitude although the 4 kHz tone responses were statistically indistinguishable across subjects [13].

A. Probe frequencies near 0.5 kHz

MOC effects near 0.5 kHz elicited by tone and NBN elicitors are shown in Figures 4 and 5, respectively. First, we will consider the magnitude of ΔSFOAE (top rows of Figs. 4 and 5) and then $SFOAE_{MOC}$ (middle and bottom rows of Figs. 4 and 5). There were significant elicitor frequency effects on the ΔSFOAE magnitude for bilateral and ipsilateral elicitors. ANOVA results are in table 2. Contralateral elicitors gave statistically significant effects when analyzed in the during-elicitor window but not in the post-elicitor window by which time most of the effect had decayed into the noise floor. Individual ΔSFOAE magnitude points that were significantly different from the noise floor (marked with asterisks in the Figures) were at least 60% of the maximum ΔSFOAE magnitude for their laterality.

Elicitor laterality had a significant effect on the ΔSFOAE magnitude (ANOVA: $P < 10^{-3}$). In general, when the ΔSFOAE magnitude for a bilateral elicitor was statistically significant, the bilateral elicitor yielded a greater effect than either the ipsilateral or contralateral elicitor. Ipsilateral ΔSFOAE magnitudes ranged from greater than the contralateral ΔSFOAE magnitude, to not statistically different, implying that the relative magnitude of ipsilateral to contralateral ΔSFOAE is dependent on elicitor frequency.

Ipsilateral and bilateral tones elicited the greatest ΔSFOAE magnitude when centered at the probe frequency while the maximum contralateral ΔSFOAE magnitude was for a tone elicitor at half an octave above the probe tone frequency (Figure 4). The patterns of ΔSFOAE magnitude versus elicitor frequency appeared slightly skewed for the contralateral elicitor but the skew was not significantly significant

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[12] ANOVA results to determine if ear orientation (left and right) has a significant effect on the ΔSFOAE magnitudes are as follows: $P_{Tone,0.5kHz} = 0.53$, $P_{NBN,0.5kHz} = 0.90$; $P_{Tone,1kHz} = 0.55$, $P_{NBN,1kHz} = 0.60$; $P_{Tone,4kHz} = 0.49$, $P_{NBN,4kHz} = 0.78$

[13] ANOVA results to determine if the inter-subject variation has a significant effect on the ΔSFOAE magnitudes are as follows: $P_{Tone,0.5kHz} < 10^{-3}$, $P_{NBN,0.5kHz} = 0.02$; $P_{Tone,1kHz} < 10^{-3}$, $P_{NBN,1kHz} < 10^{-3}$; $P_{Tone,4kHz} = 0.49$, $P_{NBN,4kHz} = 1.40 \times 10^{-3}$

(Skewness coefficients, and results from testing the hypothesis of symmetry, are in Table 3). Changes in the ΔSFOAE magnitude patterns from NBNs were qualitatively similar to those from tones, except that for NBNs large effects occurred over a wider elicitor-frequency range making the NBN-induced ΔSFOAE magnitude pattern appear less peaky. At frequencies above the probe frequency, NBN elicitors were generally more effective than tones. For all three elicitor lateralities, significant NBN-elicited ΔSFOAE magnitudes were observed over a broad elicitor-frequency range, from the probe frequency to 1 or 1.5 octaves above the probe frequency. Significant skews, with elicitor frequencies above the probe frequency being most effective, were found for NBN elicitors presented bilateral and contralaterally, but not ipsilaterally.

MOC effects considered as $\text{SFOAE}_{\text{MOC}}$, the MOC-inhibited SFOAE, are summarized in the second and third rows of Figures 4 and 5 for tone and NBN elicitors respectively. Significant SFOAE magnitude inhibition was observed for all elicitor lateralities at some elicitor frequency. ANOVA results on the effect of elicitor frequency on the magnitude and phase of $\text{SFOAE}_{\text{MOC}}$ are summarized in table 4. Inhibition of the magnitude of $\text{SFOAE}_{\text{MOC}}$ by ipsilateral and binaural tone elicitors was greatest for tones centered at the probe frequency (Fig. 4D). In contrast, inhibition by contralateral tones was greatest for tones centered half an octave above the probe frequency (Fig. 4C). NBNs elicited inhibition over a wider range of elicitor frequencies than tones, a range that included the probe frequency and frequencies above the probe (Figs. 5C and D versus Figs. 4C and D). The MOC effects on SFOAE phase, as shown by $\text{SFOAE}_{\text{MOC}}$ (last row of Figs. 4 and 5) were generally not statistically significant. However, since the tone and NBN experiments yielded independent data sets, the roughly similar patterns in phase-change versus elicitor-frequency for both tone and NBN elicitors suggests that these patterns, though not statistically significant, might be due to MOC effects and not simply a result of noise.

B. Probe frequencies near 1 kHz

MOC effects near 1 kHz are summarized in Figures 6 and 7 for tone and NBN elicitors, respectively. The figure layouts are the same as Figures 5 and 6 for 0.5 kHz. Elicitor frequency had a significant effect on ΔSFOAE magnitude for all elicitor lateralities. ANOVA results are summarized in table 2. Individual ΔSFOAE magnitude points that were significantly different from the noise floor (marked with asterisks in the Figures) were at least 60% of the maximum ΔSFOAE magnitude for their laterality.

Elicitor laterality had a significant effect on the ΔSFOAE magnitude (ANOVA: $P < 10^{-3}$). Bilateral and contralateral elicitors produced ΔSFOAE-magnitude maxima at elicitor frequencies ½ to 1 octave below the probe frequency, but ipsilateral elicitors produced a maximum when centered on the probe frequency (Figs. 6-7, top row). Statistically significant ΔSFOAE magnitudes were elicited by NBNs over a wider range than for tone elicitors, especially for elicitor frequencies above the probe. There was statistically significant skew in the ΔSFOAE magnitude towards elicitor frequencies below the probe frequency being most effective (skewness coefficients, and results from testing the hypothesis of symmetry, are in Table 3). Similar to the results at 0.5 kHz, near 1 kHz the ΔSFOAE magnitudes from bilateral elicitors were generally larger than from ipsilateral and contralateral elicitors, while the ratio of ΔSFOAE magnitudes from ipsilateral and contralateral elicitors appeared to vary as a function of elicitor frequency.

For 1 kHz probes, the magnitudes and phases of $\text{SFOAE}_{\text{MOC}}$ for tone and NBN elicitors are shown in the second and third rows of figures 6 and 7. ANOVA results on the effect of elicitor frequency are given in Table 4. The patterns of $\text{SFOAE}_{\text{MOC}}$ magnitude inhibition versus elicitor frequency were substantially different from the ΔSFOAE-magnitude-change patterns (Figs 6-7, middle versus top rows). The patterns of $\text{SFOAE}_{\text{MOC}}$ magnitude inhibition as a function of elicitor frequency were remarkably similar for tone and NBN elicitors. For both, bilateral and ipsilateral elicitors produced significant $\text{SFOAE}_{\text{MOC}}$ magnitude inhibition when centered at the probe frequency (Figs. 6D, 7D) while contralateral elicitors did not significantly inhibit the $\mathrm{SFOAE_{MOC}}$ magnitudes (Figs. 6C and 7C). For all lateralities, tone or NBN elicitors below the probe frequency produced significant $\mathrm{SFOAE_{MOC}}$ phase leads (Figs. 6-7, E & F).

C. Probe frequencies near 4 kHz

MOC effects near 4 kHz are summarized in Figures 8 and 9 for tone and NBN elicitors, respectively. The figure layouts are the same as Figures 5 and 6 for 0.5 kHz. Elicitor frequency had significant effects on the ΔSFOAE magnitude (first row of Figs. 8 and 9) for elicitors of all three lateralities. ANOVA results are summarized in table 2. Individual ΔSFOAE magnitude points that were significantly different from the noise floor (marked with asterisks in the Figures) were at least 60% of the maximum ΔSFOAE magnitude for their laterality.

Elicitor laterality had a significant effect on the ΔSFOAE magnitude (ANOVA: P=0.047). Bilateral and ipsilateral elicitors produced ΔSFOAE-magnitude maxima when the elicitor frequency was at the probe frequency (Figs. 8B and 9B), but the during-elicitor contralateral ΔSFOAE magnitude was bimodal and exhibited a major peak effect at 0.5 octaves above the probe frequency and a broader minor peak in response to tone elicitors between 3.5 to 1.5 octaves below the probe frequency (Figs. 8A and 9A). NBNs were generally more effective than tones at eliciting significant ΔSFOAE-magnitude changes above the probe frequency. Similar to the ΔSFOAE magnitudes near 0.5 and 1 kHz, near 4kHz the ΔSFOAE magnitudes from bilateral elicitors were generally larger than from ipsilateral and contralateral elicitors, while the ratio of ΔSFOAE magnitudes from ipsilateral and contralateral elicitors appeared to vary as a function of elicitor frequency. Because there were not enough data above the probe frequency, the test for asymmetry was not carried out for data near 4 kHz[14].

For 4 kHz probes, ipsilateral and bilateral tones and NBNs elicited significant $\mathrm{SFOAE_{MOC}}$ magnitude inhibition when the elicitor was at the probe frequency (Figs. 8D and 9D). Significant phase leads in the $\mathrm{SFOAE_{MOC}}$ were elicited with ipsilateral and bilateral NBNs centered at the probe frequency and at half an octave above (Fig. 9F) but not at any tone elicitor frequency (Fig. 8F). Contralateral tone and NBN elicitors induced a significant phase lead in $\mathrm{SFOAE_{MOC}}$ measured in the during-elicitor window for a few elicitor frequencies above and below the probe frequency (Figs. 8E and 9E) but were ineffective at eliciting significant inhibition in the $\mathrm{SFOAE_{MOC}}$ magnitude (Figs. 8-9, C and D). ANOVA results on the effect of center frequencies on the magnitude and phase of $\mathrm{SFOAE_{MOC}}$ are shown in table 4.

D. Strength of MOC effects (ΔSFOAE magnitudes) as a function of probe frequencies

Our goal here was to compare the strength of the MOC effect across probe frequencies using a metric that was not too confounded by points with poor SNRs. For each probe frequency, elicitor laterality and elicitor type, we started with the highest point in the average plot of ΔSFOAE magnitude versus elicitor frequency (as shown in Figs. 4-9), and included in the group the highest point and all of the points that were not statistically significantly different from this highest point. The magnitudes of the ΔSFOAE of these points were averaged, and the magnitude of the result was plotted in Figure 10. The results were remarkably similar for tones and NBN elicitors. The MOC-effect strength for all lateralities decreased as a function of probe frequency. The MOC-effect strength was largest for bilateral elicitors followed by ipsilateral elicitors and then contralateral elicitors.

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[14] Since skew calculation about the probe makes use of data over a symmetric range above and below the probe frequency, the broad low-frequency region below 1 octave below the probe in which elicitors evoke significant effects on ΔSFOAE would not be taken into consideration.

	ANOVA (Elicitor Effect): P-values							
Probe Tone Frequency	Bilateral MOC Effect		Ipsilateral MOC Effect		Contra MOC Effect (Post-Elic)		Contra MOC Effect (During-Elic)	
	Tone	NBN	Tone	NBN	Tone	NBN	Tone	NBN
~0.5kHz -3 to +2 oct	**$< 10^{-3}$**	**$< 10^{-3}$**	**$< 10^{-3}$**	**$< 10^{-3}$**	0.32	0.07	**$< 10^{-3}$**	**$< 10^{-3}$**
~1.0kHz -2.5 to +2.5 oct	**$< 10^{-3}$**	**$< 10^{-3}$**	**$< 10^{-3}$**	**$< 10^{-3}$**	**$< 10^{-3}$**	**$< 10^{-3}$**	**$< 10^{-3}$**	**$< 10^{-3}$**
~4.0kHz -3.5 to +1 oct	**$< 10^{-3}$**	**$1.30\text{x}10^{-3}$**	**$9.60\text{x}10^{-3}$**	**$< 10^{-3}$**	0.43	0.63	**$1.01\text{x}10^{-2}$**	**$6.90\text{x}10^{-3}$**

Table 2: ANOVA results of the effect of elicitor frequency on ΔSFOAE magnitude. Significance is taken at probability $P \leq 0.05$. Significant values are shown in bold letters. The data are plotted in Figures 4-9.

Probe Tone Frequency		Bilateral		Ipsilateral		Contralateral (Post-Elic)		Contralateral (During-Elic)	
		Tone	NBN	Tone	NBN	Tone	NBN	Tone	NBN
~0.5kHz [-2 to 2 oct]	Pearson's Skewness Factor, **b_1**	0.12	**-0.18**	0.01	-0.08	0.08	**-0.27**	-0.07	**-0.37**
	$\hat{P}_{b_1}$	0.06	**0.97**	0.43	0.19	0.19	**0.98**	0.78	**0.99**
~1.0kHz [-2.5 to2.5 oct]	Pearson's Skewness Factor, **b_1**	**0.41**	**0.29**	**0.25**	**0.19**	**0.38**	**0.19**	**0.53**	**0.23**
	$\hat{P}_{b_1}$	**$< 10^{-3}$**	**$< 10^{-3}$**	**$4\text{x}10^{-3}$**	**0.03**	**$< 10^{-3}$**	$< 10^{-3}$	**0.00**	**$6.60\text{x}10^{-3}$**

Table 3: Summary of asymmetry measures for the ΔSFOAE magnitude to bilateral, ipsilateral and contralateral, 60 dB SPL, tone and NBN elicitors. Asymmetry was quantified by the skewness factor where zero signifies perfect symmetry about the mean, positive skewness factors are indicative of a response bias towards lower frequencies (left of the mean) and vice versa. The significance of the skewness factors being different from 0 was tested using a bootstrapped distribution under the null hypothesis of symmetry. The hypothesis test results are summarized here as $\hat{P}_{b_1}$. Significance was taken at tail-probability values of $P \leq 0.05$. Data are shown in Figures 4-7.

		Bilateral SFOAE$_{MOC}$		Ipsilateral SFOAE$_{MOC}$		Contralateral SFOAE$_{MOC}$ (Post-Elicitor)		Contralateral SFOAE$_{MOC}$ (Steady-State)	
Probe Freq.	Elicitor Type	Mag.	Phase	Mag.	Phase	Mag.	Phase	Mag.	Phase
~0.5 kHz	Tone	**< 10^{-3}**	0.85	**0.002**	0.91	0.29	0.26	**0.03**	0.99
	NBN	**< 10^{-3}**	0.80	**0.002**	**0.04**	0.15	0.06	**< 10^{-3}**	0.13
~1.0 kHz	Tone	**0.005**	**< 10^{-3}**	**< 10^{-3}**	**< 10^{-3}**	0.31	**0.007**	0.98	**0.002**
	NBN	**0.01**	**< 10^{-3}**	**< 10^{-3}**	**< 10^{-3}**	0.69	**< 10^{-3}**	0.82	**< 10^{-3}**
~4.0 kHz	Tone	**< 10^{-3}**	0.60	**< 10^{-3}**	0.87	0.11	0.52	0.47	**0.007**
	NBN	**< 10^{-3}**	**< 10^{-3}**	**< 10^{-3}**	0.37	0.78	0.42	0.23	**0.006**

Table 4: ANOVA results on the effect of the elicitor frequencies on the magnitude and phase of the remaining SFOAE$_{MOC}$. Significance is taken at tail-probability values, $P \leq 0.05$ and is recorded by bold letters. Data are shown in Figures 4-9.

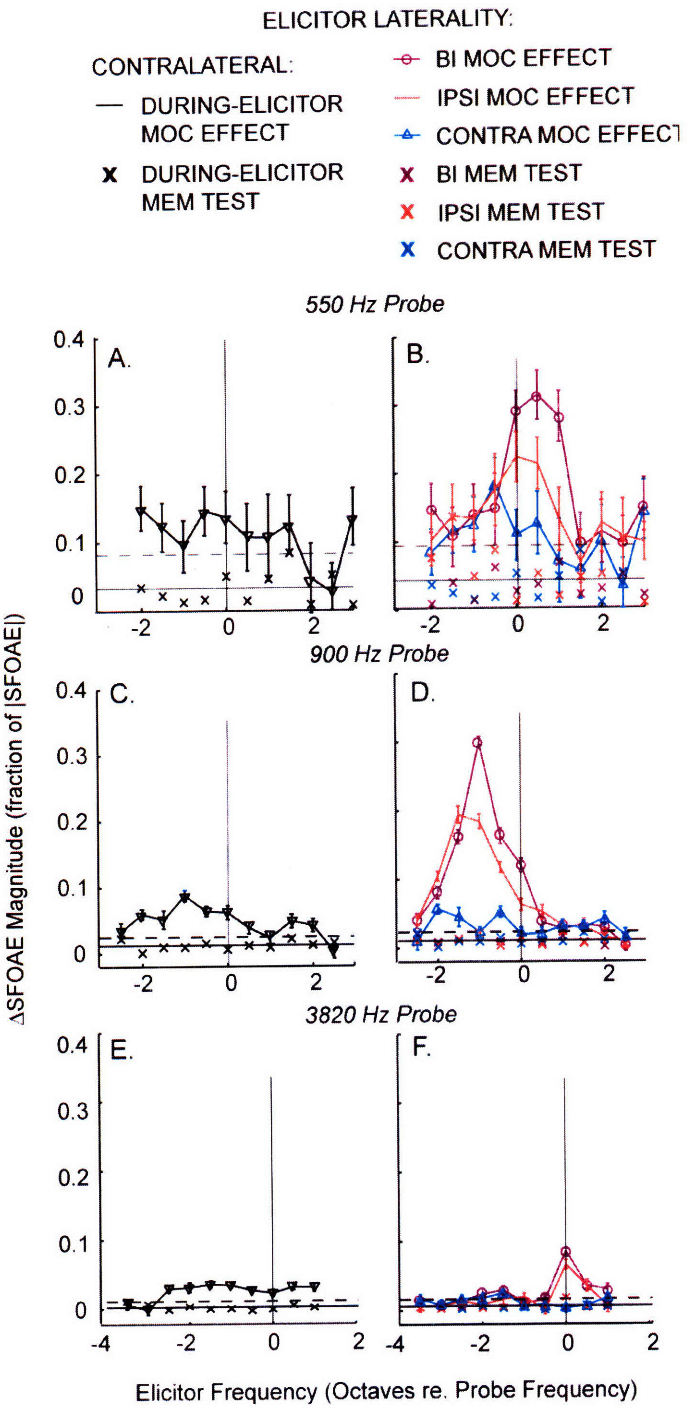

Figure 3. Data from one subject showing examples of ΔSFOAE magnitudes to NBN elicitors (symbols with error bars) as functions of elicitor frequency, and corresponding MEM responses (X's). The elicitors were 60 dB SPL, half-octave NBNs and the probe frequencies were near 0.5, 1 and 4 kHz (top to bottom). Left column: ΔSFOAE magnitudes to contralateral elicitors measured in a 100-ms during-elicitor window that ended 50 ms prior to elicitor offset (black: ∇). Right column: ΔSFOAE magnitudes to Bilateral (purple: O), Ipsilateral (red: —) and Contralateral (blue Δ) elicitors measured in a post-elicitor window (100 ms duration starting 50 ms after elicitor offset. Black Lines: Solid = noise-floor mean, dashed = 2 standard deviations above the noise mean. Note that the MEM-test measures were generally within 2 standard deviations of the noise floor.

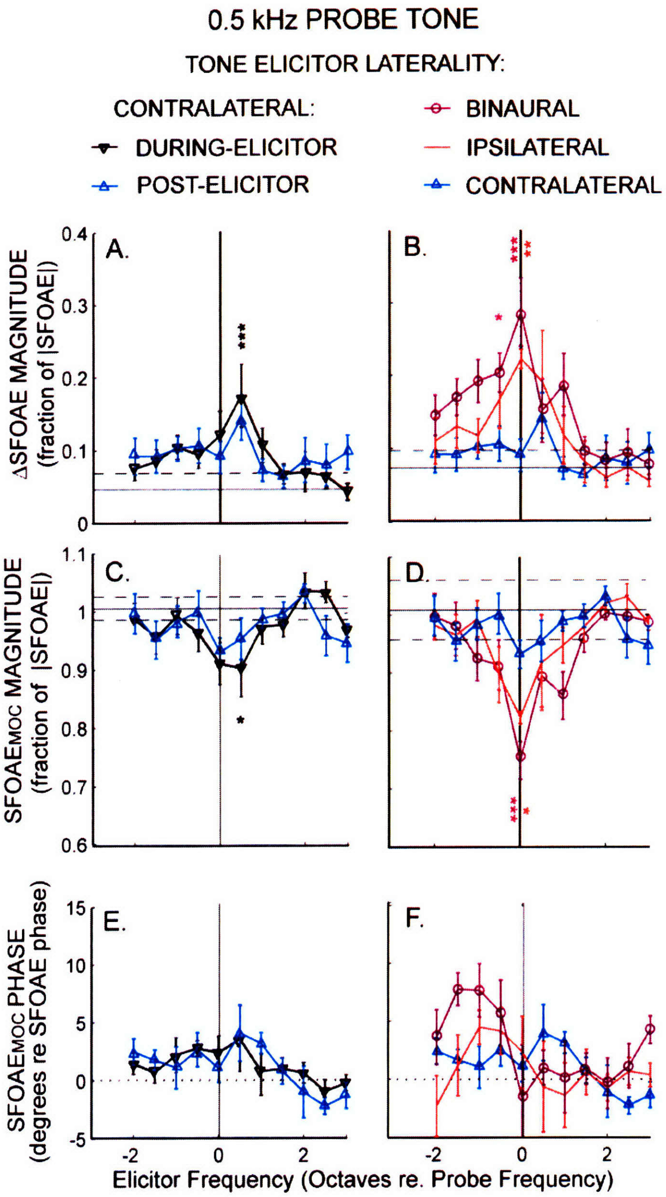

Figure 4. Magnitude of ΔSFOAE (top) near 0.5 kHz in response to Tone elicitors (symbols with error bars) as functions of elicitor frequencies and the remaining SFOAE$_{MOC}$ magnitudes (2nd Row) and phases (3rd Row) from the elicitor-induced change. Left column: Responses to the same contralateral elicitors as at right except measured in a during-elicitor window (0.4 s duration starting 0.45 s before elicitor offset) are shown in black (∇ with error bars). Right column: Effects to Bilateral (purple: O), Ipsilateral (red: —) and Contralateral (blue: Δ) 60 dB SPL tone elicitors measured in a post-elicitor window (0.1 s duration starting 0.05 s after elicitor offset). Black horizontal lines: Solid = noise-floor mean, dashed = 1 std above the noise mean. Significant differences (Students' t-test with a Bonferroni correction for multiple comparisons) from the control (noise floor) are marked with asterisks: '*' ($P \leq 0.05$), '**' ($P \leq 0.01$), '***' ($P \leq 0.001$).

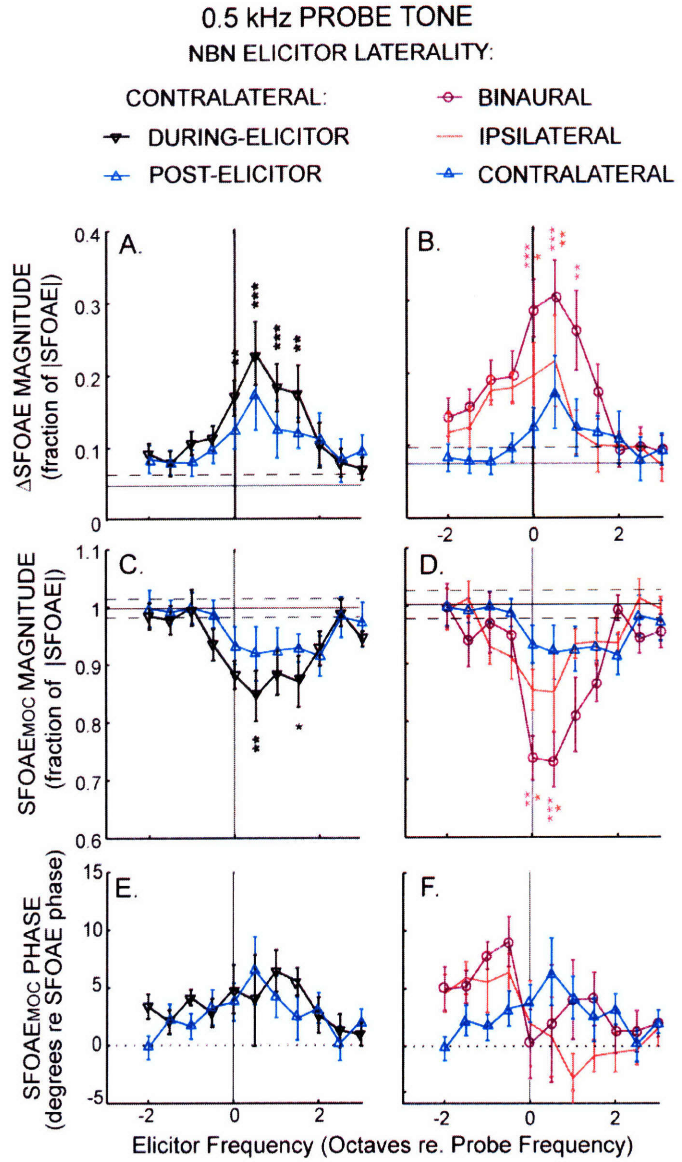

Figure 5. Magnitude of ΔSFOAE (top) near 0.5 kHz in response to NBN elicitors (symbols with error bars) as functions of elicitor frequencies and the remaining $\mathrm{SFOAE_{MOC}}$ magnitudes (2^{nd} Row) and phases (3^{rd} Row) from the elicitor-induced change. Left column: Responses to the same contralateral elicitors as at right except measured in a during-elicitor window (0.4 s duration starting 0.45 s before elicitor offset) are shown in black (∇ with error bars). Right column: Effects to Bilateral (purple: O), Ipsilateral (red: —) and Contralateral (blue: Δ) 60 dB SPL tone elicitors measured in a post-elicitor window (0.1 s duration starting 0.05 s after elicitor offset). Black horizontal lines: Solid = noise-floor mean, dashed = 1 std above the noise mean. Significant differences (Students' t-test with a Bonferroni correction for multiple comparisons) from the control (noise floor) are marked with asterisks: '*' ($P \leq 0.05$), '**' ($P \leq 0.01$), '***' ($P \leq 0.001$).

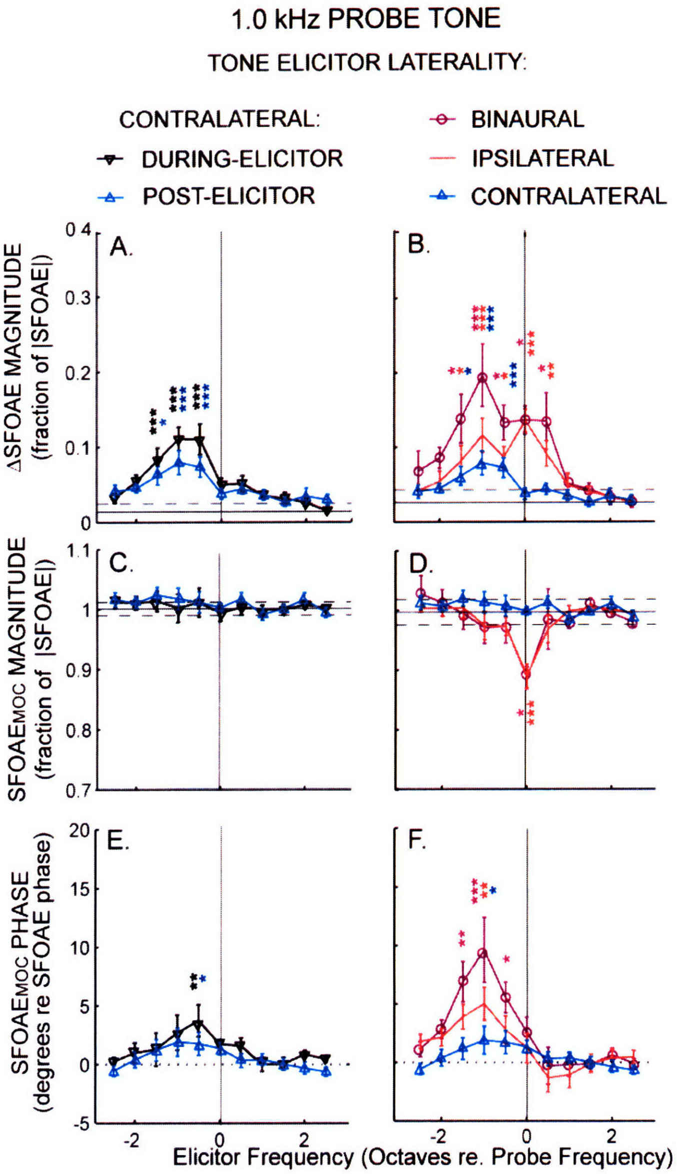

Figure 6. Magnitude of ΔSFOAE (top) near 1 kHz in response to Tone elicitors (symbols with error bars) as functions of elicitor frequencies and the remaining $\text{SFOAE}_{\text{MOC}}$ magnitudes (2nd Row) and phases (3rd Row) from the elicitor-induced change. Left column: Responses to the same contralateral elicitors as at right except measured in a during-elicitor window (0.4 s duration starting 0.45 s before elicitor offset) are shown in black (∇ with error bars). Right column: Effects to Bilateral (purple: O), Ipsilateral (red: —) and Contralateral (blue: Δ) 60 dB SPL tone elicitors measured in a post-elicitor window (0.1 s duration starting 0.05 s after elicitor offset). Black horizontal lines: Solid = noise-floor mean, dashed = 1 std above the noise mean. Significant differences (Students' t-test with a Bonferroni correction for multiple comparisons) from the control (noise floor) are marked with asterisks: '*' ($P \leq 0.05$), '**' ($P \leq 0.01$), '***' ($P \leq 0.001$).

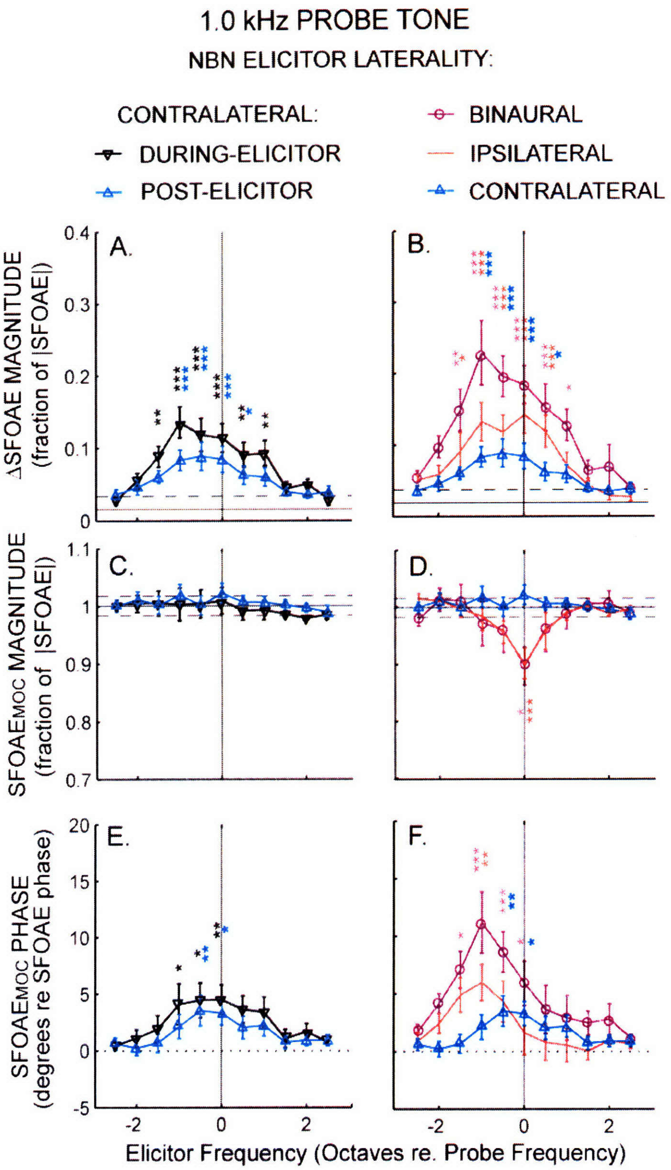

Figure 7. Magnitude of ΔSFOAE (top) near 1 kHz in response to NBN elicitors (symbols with error bars) as functions of elicitor frequencies and the remaining $\text{SFOAE}_{\text{MOC}}$ magnitudes (2^{nd} Row) and phases (3^{rd} Row) from the elicitor-induced change. Left column: Responses to the same contralateral elicitors as at right except measured in a during-elicitor window (0.4 s duration starting 0.45 s before elicitor offset) are shown in black (∇ with error bars). Right column: Effects to Bilateral (purple: O), Ipsilateral (red: —) and Contralateral (blue: Δ) 60 dB SPL tone elicitors measured in a post-elicitor window (0.1 s duration starting 0.05 s after elicitor offset). Black horizontal lines: Solid = noise-floor mean, dashed = 1 std above the noise mean. Significant differences (Students' t-test with a Bonferroni correction for multiple comparisons) from the control (noise floor) are marked with asterisks: '*' ($P \leq 0.05$), '**' ($P \leq 0.01$), '***' ($P \leq 0.001$).

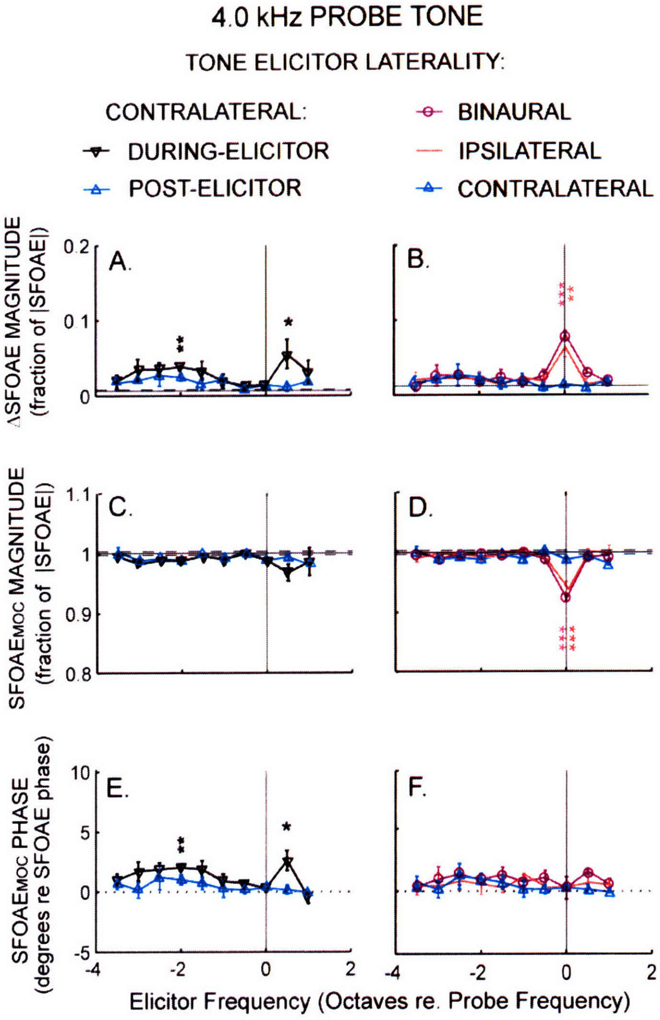

Figure 8. Magnitude of ΔSFOAE (top) near 4 kHz in response to Tone elicitors (symbols with error bars) as functions of elicitor frequencies and the remaining $\text{SFOAE}_{\text{MOC}}$ magnitudes (2nd Row) and phases (3rd Row) from the elicitor-induced change. Left column: Responses to the same contralateral elicitors as at right except measured in a during-elicitor window (0.4 s duration starting 0.45 s before elicitor offset) are shown in black (∇ with error bars). Right column: Effects to Bilateral (purple: O), Ipsilateral (red: —) and Contralateral (blue: Δ) 60 dB SPL tone elicitors measured in a post-elicitor window (0.1 s duration starting 0.05 s after elicitor offset). Black horizontal lines: Solid = noise-floor mean, dashed = 1 std above the noise mean. Significant differences (Students' t-test with a Bonferroni correction for multiple comparisons) from the control (noise floor) are marked with asterisks: '*' (P≤0.05), '**' (P≤0.01), '***' (P≤0.001).

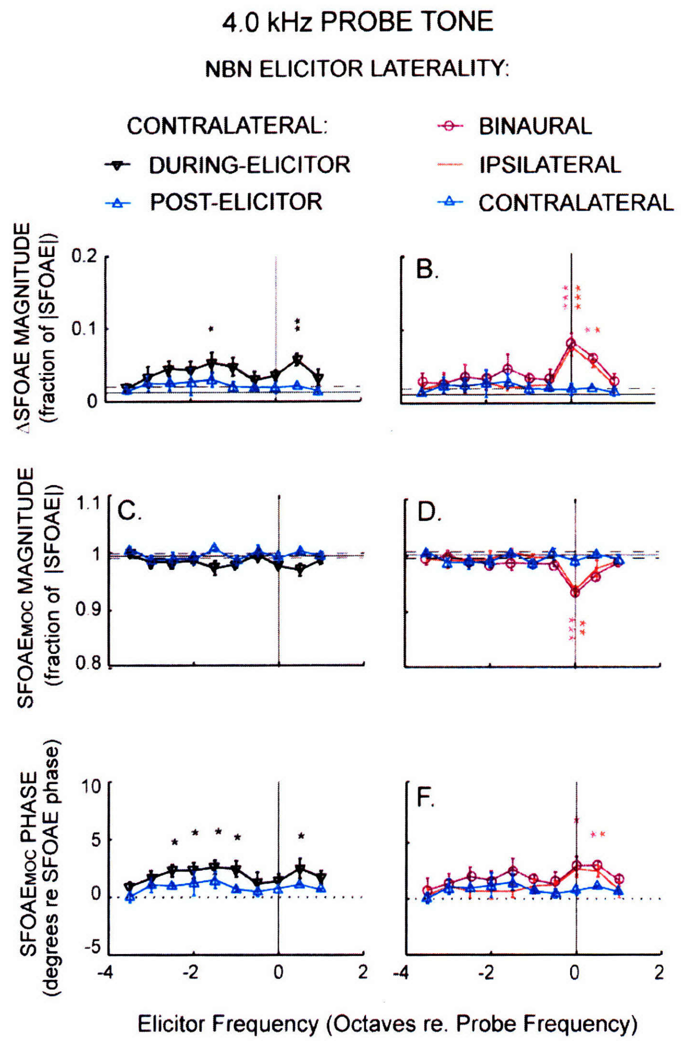

Figure 9. Magnitude of ΔSFOAE (top) near 4 kHz in response to NBN elicitors (symbols with error bars) as functions of elicitor frequencies and the remaining SFOAE$_{MOC}$ magnitudes (2nd Row) and phases (3rd Row) from the elicitor-induced change. Left column: Responses to the same contralateral elicitors as at right except measured in a during-elicitor window (0.4 s duration starting 0.45 s before elicitor offset) are shown in black (∇ with error bars). Right column: Effects to Bilateral (purple: O), Ipsilateral (red: —) and Contralateral (blue: Δ) 60 dB SPL tone elicitors measured in a post-elicitor window (0.1 s duration starting 0.05 s after elicitor offset). Black horizontal lines: Solid = noise-floor mean, dashed = 1 std above the noise mean. Significant differences (Students' t-test with a Bonferroni correction for multiple comparisons) from the control (noise floor) are marked with asterisks: '*' ($P \leq 0.05$), '**' ($P \leq 0.01$), '***' ($P \leq 0.001$).

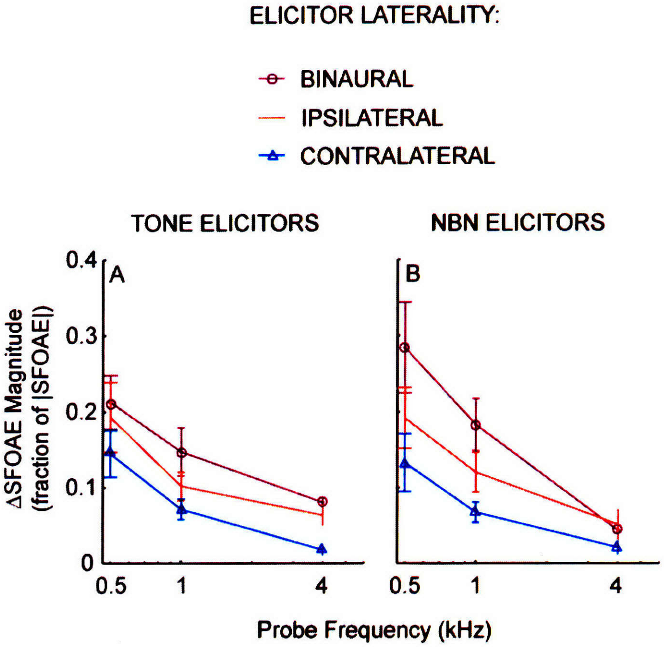

Figure 10. Average peak MOC effect magnitude is a decaying function of probe frequency for all tone (A) or NBN (B) elicitor lateralities: ipsilateral (red: —), contralateral (blue: Δ) and bilateral (purple: O). The number of subject ears averaged for 0.5 kHz, 1 kHz and 4 kHz were 8, 11 and 3 respectively. Error bars represent 1 standard error of the mean.

IV. Discussion

Data and Methods Considerations

A notable feature of our data is that the magnitude of ΔSFOAE was largest for 500 Hz probes, intermediate for 1 kHz probes and smallest for 4 kHz probes (Fig. 10). This progression was found for tone and NBN elicitors and for all elicitor lateralities. The interesting thing about this progression is that it goes in the opposite direction from the density of MOC innervation in humans (Schrott-Fischer et al., 1994). Thus it appears that the progression must be due to the pattern of sound activation of MOC fibers, greater sound elicited activation for fibers to more apical parts of the cochlea.

The low response magnitude at 4 kHz was the main cause of perhaps the greatest weakness of the present study, that there were only 3 subjects at 4 kHz. The SNR of MOC effects on SFOAEs depends on the magnitude of the raw ΔSFOAE (ΔSFOAE before normalization by |SFOAE|) and the magnitude of the background noise which is mostly microphone noise. Both the noise and the (normalized) ΔSFOAE increase as frequency decreases, while |SFOAE| is generally largest at 1-2 kHz, with the result that the best SNR is at 1 kHz and the worst is at 4 kHz. Because of this, it is difficult to find subjects with good enough SNRs at 4 kHz to make these measurements. One factor that partially ameliorates the small number of subjects is that they all had relatively similar response patterns, in particular, the MOC-effect patterns for tone elicitors were not significantly different[4].

Our analysis revealed that MOC-induced magnitude and phase changes of $\text{SFOAE}_{\text{MOC}}$ do not always occur together. The MOC effects elicited by ipsilateral and bilateral elicitors at frequencies near the probe frequency resulted predominantly in the inhibition of SFOAE magnitudes. In contrast, MOC effects from contralateral elicitors generally showed only small inhibitions of SFOAE magnitudes, but showed significant phase changes, particularly for elicitor frequencies remote from the probe frequency. That the magnitude reduction and phase leads do not always occur together was unexpected. These observations suggest that the mechanism and effect of near-probe-frequency MOC effects versus remote off-probe-frequency MOC effects might be fundamentally different. However, an alternate explanation is offered below. In addition, the differences in the pattern of MOC effects, both in terms of ΔSFOAE magnitude or $\text{SFOAE}_{\text{MOC}}$, from ipsilateral and contralateral elicitors suggests a difference in the physiological organization of these reflexes.

Overview of amplitude and phase changes in SFOAEs

When we started this work, the question, "How do MOC effects vary across elicitor frequency at different probe frequencies?" was based on the conception that there was only one MOC effect, inhibition (at least for MOC fast effects, Cooper and Guinan 2003). Almost all of the detailed knowledge about MOC effects has come from shock-evoked MOC activity which excites MOC fibers evenly across fiber BFs – judging from the close correspondence of the pattern of MOC innervation along the length of the cochlea to the pattern of MOC inhibition of auditory-nerve responses as a function of fiber CF (Guinan and Gifford 1988). These shock-evoked MOC effects showed clear patterns of inhibition in auditory nerve fiber responses, but revealed no pattern in the phase changes (Gifford and Guinan, 1983). Animal studies show that MOC-fiber TCs are tuned approximately like AN-fiber TCs (at least at their tips) and innervate restricted, approximately tonotopically-appropriate regions in the cochlea (Liberman and Brown, 1986; Brown 1989; Robertson 1984, 1985). Thus, sound-evoked MOC effects are expected to show an inhibition focused along the cochlear frequency axis with the greatest effects for elicitor frequencies near the probe frequency. SFOAEs are the most frequency selective OAE, but are not as frequency selective as the response of an auditory-nerve fiber. SFOAEs summate MOC effects over the region where the traveling wave envelope of the probe tone is large (Shera and Zweig, 1993b; Zweig and Shera, 1995). MOC effects on SFOAEs have been studied with MOC activity elicited by shocks or by broad-band noise. However, this is the first study to examine phase changes in SFOAEs (or in any OAE), and perhaps more importantly, the first to study phase changes with an elicitor expected to produce a focused pattern of MOC activation. Since SFOAE phase is a weighted sum of back-scattered wavelets from the traveling wave of the probe tone, changes in these weightings due to a focused pattern of MOC inhibition may cause changes in the resulting SFOAE phase. One interpretation (explained more in the Mechanisms section, below) is that MOC-induced changes in SFOAE phase are due to MOC inhibition focused at an edge of the traveling-wave peak region, which shifts the balance of the phase contributions from along the traveling wave, resulting in a change of the overall phase. Thus, the MOC-induced phase changes seen in $\mathrm{SFOAE}_{\mathrm{MOC}}$ may still be due to MOC inhibition, but inhibition that changes the envelope of the traveling wave, or shifts its position along the cochlea. This interpretation of the phase changes needs more direct evidence before it is accepted, nonetheless, it serves as a useful way to think about what the MOC-induced phase change of the $\mathrm{SFOAE}_{\mathrm{MOC}}$ may mean.

Comparison with prior work

There are two previous reports on the frequency specificity of the MOC reflex in humans (Vieullet et al., 1991; Chery-Croze et al., 1993). These studies used transient evoked otoacoustic emissions (TEOAEs) from tone pips, and distortion product otoacoustic emissions (DPOAEs), respectively. In both, the MOC effect was quantified as the OAE amplitude suppression produced by the MOC elicitor. At first glance, the magnitude of $\mathrm{SFOAE}_{\mathrm{MOC}}$, which is expressed as a fraction relative to the original SFOAE magnitude, appears to correspond to the amplitude-ratio metrics used by these studies (i.e. the original DPOAE amplitude minus the MOC-inhibited DPOAE amplitude, both in dB SPL). The DPOAE and TEOAE metrics look only at amplitudes, with phase effects seemingly ignored. However, the MOC-induced change in the DPOAE is a complex statistic because the DPOAE is made up of two components (Kalluri and Shera, 2001) and these components may be affected by MOC activity in different ways. Since the two components sum vectorially, a change in the phase or amplitude of one component can change the overall DPOAE amplitude. The DPOAE amplitude is especially sensitive to component phase changes in regions near a dip in the DPOAE response where the two components nearly cancel. Although this region was not used by Chery-Croze et al., it has become the preferred place to measure MOC effects because large MOC-induced changes in DPOAE amplitude are produced there (Wagner et al., 2007). The large MOC-induced changes in DPOAE amplitudes seen near dips are particularly likely to be affected by small changes in the phase of one component, but MOC-induced phase changes can influence the amplitude of all DPOAE measurements. Thus, DPOAE amplitude change may be more like our ΔSFOAE metric in that both show changes in the amplitude or the phase of the underlying components. MOC effects on TEOAEs, as used by Vieullet et al., may also be susceptible to changes in the phase of the underlying wavelet components. For instance, a signal made up of multiple tones, all with the same phase, will have a large, peaked response compared to a signal made up of the same tone amplitudes but random phases.

Both Vieullet et al. (1991) and Chery-Croze et al. (1993) used 1/3 octave narrow-band noise elicitors at various frequencies relative to the probe frequency[15]. Both reported statistically significant MOC effects for 1 and 2 kHz probes (tone-pip frequency, and DPOAE frequency, respectively). Both reports emphasize that the largest MOC effects were produced by elicitors close in frequency to the probe frequency, but both show examples of elicitor frequencies approximately ½ octave below the probe being most effective for 2 kHz probes. Chery-Croze et al. show data from a subject in whom elicitors 2 octaves below the probe produced significant MOC inhibition. Their results from 1 and 2 kHz look asymmetric with elicitor frequencies below the probe frequency being more effective than elicitor frequencies above

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[15] Chery-Croze et al. (1993) did not specify the bandwidth of their narrow-band-noise. However, since these two studies came from the same place and the other specifications of the noise are the same, it seems likely that Chery-Croze et al. used the same 1/3 octave narrow-band-noise as did Vieullet et al. (1991).

the probe, but no asymmetry test was done. The MOC-effect measures used by these two studies are sufficiently different from ours that a detailed comparison of results is not possible. However, their results are consistent with ours in showing significant MOC effects can be produced by elicitors centered an octave or more from the probe frequency.

One important aspect of the results of Vieullet et al. (1991) and Chery-Croze et al. (1993) does not appear to agree with ours, namely, they found significant amplitude reductions produced by contralateral sound, whereas with contralateral sound, we did not find amplitude reductions, at least as measured by the MOC-induced change in $SFOAE_{MOC}$ (Figs. 6C, 7C). However, we did see contralaterally-elicited magnitude changes when measured by ΔSFOAE, a metric that includes both the amplitude and phase changes of the $SFOAE_{MOC}$. Thus, the fact that Vieullet et al. and Chery-Croze et al. found contralaterally-induced changes in their OAE metrics can be taken as evidence that these metrics include both amplitude and phase changes of the underlying OAE components.

Finally, our finding that the MOC-induced changes in $SFOAE_{MOC}$ are mostly phase advances is consistent with studies that reported reduced OAE latencies from MOC activation (Ryan, 1991; Giraud et al. 1995, 1996). Our phase advances also are consistent with the finding that shock stimulation of MOC efferents in guinea pigs produces a slight reduction of the latency of basilar-membrane click responses (Guinan and Cooper, submitted).

Mechanisms by which $SFOAE_{MOC}$ phase and amplitude changes may be produced

The most important thing to know about our metrics, ΔSFOAE and $SFOAE_{MOC}$, is their correspondence with the MOC effect on neural responses. Unfortunately, that correspondence is not known for SFOAEs, or any OAE. However, in a previous study by Warren and Liberman (1989a, b), the inhibitory effects of 70 dB SPL contralateral tone elicitors on the firing rate of auditory nerve fibers in cats for units with CF near 2 kHz showed that: 1) MOC-inhibition of auditory nerve fibers by contralateral tones were skewed to frequencies below the probe. 2) MOC-inhibition of the auditory nerves could be elicited over roughly a 1.5 octaves below and 1 octave above the fiber's CF. These patterns from the cat strike remarkable similarities to our human ΔSFOAE magnitude results at 1 kHz to contralateral tones. When ΔSFOAE was decomposed into the magnitude inhibition and phase lead of the $SFOAE_{MOC}$, we found insignificant magnitude inhibitions but significant phase changes (leads) in the $SFOAE_{MOC}$ due to contralateral tone elicitors. Hence, phase changes were the dominant contributing factor to the contralateral ΔSFOAEs at 1 kHz. Presuming that the Warren and Liberman (1989b) results from anesthetized cats apply to awake humans, these results suggest that ΔSFOAE magnitudes correspond better to auditory-nerve inhibitions than $SFOAE_{MOC}$ magnitudes. Although the SFOAE may be the simplest OAE and the easiest to interpret in terms of underlying changes in the cochlea, it appears that interpreting changes in SFOAEs is not simple.

The change in SFOAE phase may still be behaviorally important, e.g. in binaural sound localization. For instance, the relatively weak MOC activation produced by our 60 dB SPL, half-octave bands of noise was enough to change the $SFOAE_{MOC}$ phase by 10 degrees at 1 kHz, a behaviorally detectable difference if it occurred in one ear but not the other. It might be thought that prevention of such a phase difference between the two ears may be a reason for having a binaurally-balanced MOC system, i.e. for having the MOC system produce the same effect in both ears even if the sound stimulus is mostly on one side. In the apex, the MOC innervation density from the two sides is approximately equal whereas in the base it is heavily biased toward fibers of the ipsilateral MOC reflex (Guinan et al., 1984; Guinan 1996). Against this hypothesis, however, is the fact that the phase changes produced by the contralateral and ipsilateral reflexes are often quite different (Figs. 3-9).

At the heart of interpreting MOC-induced changes in the amplitude and phase of $\text{SFOAE}_{\text{MOC}}$, is understanding what underlying cochlear mechanical changes produce these changes. According to coherent reflection theory, the SFOAE comes from random backscattering of the traveling wave (Shera and Zweig, 1993b; Zweig and Shera, 1995). The SFOAE amplitude depends on the amplitude of the traveling wave and how the various backscattered wavelets add together, and the phase of the SFOAE depends on the phase of the traveling wave weighted by the backscattered waves. Thus, if the shape of the envelope of the traveling wave was changed by MOC stimulation, it might change the SFOAE phase without there being a substantial change in the magnitude of the SFOAE. Measurements and theory show that the traveling wave slows down as it proceeds apically, which means that the slope of the traveling wave phase becomes steeper as a function of cochlear position going in the apical direction. If MOC stimulation selectively inhibited the more apical part of the traveling wave (e.g. due to an elicitor at a lower frequency than the probe sound) then high-phase-slope (i.e. long group-delay) components of the SFOAE might be selectively reduced and the resultant SFOAE would have a net reduced phase delay, i.e. the SFOAE would show a phase advance. The opposite might be expected to happen for MOC stimulation that selectively inhibited the most basal part of the traveling wave response, i.e. such inhibition might result in an increased phase delay. This pattern of more apical elicitors producing a phase advance and more basal elicitors producing a phase delay is approximately the pattern of phase changes seen in much of the actual data, particularly the $\text{SFOAE}_{\text{MOC}}$ phase changes from ipsilateral elicitors and 0.5 and 1 kHz probes (Figs. 4-7).

If the above analysis, or something like it, is correct, then the $\text{SFOAE}_{\text{MOC}}$ phase change can be thought of as being a result of a shift in the pattern of the traveling wave. Since most of the phase changes are phase advances, the shift is generally toward the base. This analysis suggests that the $\text{SFOAE}_{\text{MOC}}$ phase change would have different behavioral consequences than a $\text{SFOAE}_{\text{MOC}}$ magnitude change. Of course, at this time, the above explanation must be considered as speculative. A first step in determining whether this explanation is correct would be an exploration of the effect of a hypothetical focused MOC inhibition in a distributed cochlear model of the kind used to simulate the production of SFOAEs, such as the model of Shera et al. (2005).

Comparison with psychophysical studies across probe frequencies

The MOC reflex has been hypothesized to improve signal detection in the presence of background noise which can mask the signal. Simultaneous masking can be due to two different peripheral mechanisms: (1) two-tone suppression of the mechanical (Ruggero et al., 1992) and neural response (Sachs and Kiang, 1968) to the signal by the masker and (2) to the spread of excitation by the masker to the signal place along the cochlea (Wegel and Lane, 1924; Egan and Hake, 1950). The two processes are not mutually exclusive. Most studies that attempt to study the contributions of suppressive versus excitatory masking separated the two mechanisms by comparing results from non-simultaneous and simultaneous masking paradigms. Because two-tone suppression requires the simultaneous presentation of two stimuli, it cannot contribute to non-simultaneous masking as the signal and masker do not overlap temporally. In cats, Delgutte (1990a, 1996) reported that suppressive masking was strong when the masker frequency was *well below* the signal frequency while excitatory masking was predominant when the masker was presented at low levels and when it was *closer in frequency* to the signal. Other studies in humans also produced results that indicate that suppression plays a major role for masker frequencies well below the signal (Moores and Vickers, 1997; Oxenham and Plack, 1998) and little to no role when the masker frequency is close to a signal frequency (Moore and Glasberg, 1982b; Weber, 1983). In a study by Gifford and Bacon (2000) the relative contributions of suppression and excitation to simultaneous masking was reported to change as a function of signal (probe) frequency and the masker-to-signal frequency relation in humans. The study investigated the effects of a range of masker frequencies both above and below signal frequencies which were at 0.75, 2 and 4.85 kHz. The results revealed that the contribution of suppression on masking increased with increasing signal frequency – a result consistent with stronger nonlinear processing at higher rather than at lower frequencies. Specifically, the effect of suppressive masking was found to be absent at 0.75 kHz but dominant at 4.85 kHz for all maskers. Hence, at the low frequency site of 0.75 kHz, results suggested that simultaneous masking was mainly due to excitation both in the off-frequency and on-frequency region. Lastly, the authors reported that with the 2 kHz and 4.85 kHz signals, maskers above the signal resulted in a level of suppressive masking that was at least as much and sometimes even more than maskers below.

Our results reveal that the peak MOC reflex strength, quantified by the ΔSFOAE magnitude, was greatest for the lowest frequency probe (0.5 kHz), followed by the mid-frequency probe (1 kHz) and was smallest for the high frequency probe (4 kHz). According to the findings reported by Gifford and Bacon (2000), it is likely that contribution to masking is predominantly excitatory near 0.5 kHz, both excitatory and suppressive near 1 kHz and predominantly suppressive near 4 kHz. If we assume these masking contributions for the three probe frequencies are correct, and make a further assumption that the MOC reflex strength reflects the need for its effects on the cochlear mechanics to improve audition, then the implication is that the MOC effect predominantly targets the alleviation of excitatory masking. That is, near 4 kHz the MOC reflex strength is relatively small because there is little need to turn on the MOC efferents to prevent excitatory masking, because excitatory masking contributes little to masking at high probe (listening) frequencies. In contrast, near 1 kHz excitatory masking is stronger so a larger reflex strength was observed as compared to the reflex near 4 kHz. And since masking at 0.5 kHz is likely to be predominantly excitatory, the MOC reflex strength is largest.

Near 1 kHz and 4 kHz, significant MOC effects were observed in response to elicitors below the probe, especially contralateral elicitors. It is possible that the organization of the MOC effects towards lower frequency regions reflects the efferent system's importance in listening conditions where the upward spread of masking is significant. The upward spread of masking refers to the higher growth rate of masking for maskers lower in frequency than the signal. Results from a study by Yasin and Plack (2005) showed that suppression had a minimal effect on the slope of the masking function at mid-level signals (35-60 dB SPL) and that upward spread of masking was mainly determined by the compressive BM response to the signal in relation to the lower-frequency masker. Efferent activation can reduce the compressiveness of the BM response to mid-level stimuli (e.g. Dolan et al., 1997; Cooper and Guinan, 2003) and increase the incremental discharge rate in response to an incremental increase in probe intensity - thereby improving the afferent output's signal-to-noise (Kawase et al., 1993).

V. Conclusion

The overall change in the SFOAE produced by MOC stimulation, ΔSFOAE, varied with probe frequency, elicitor laterality, elicitor frequency and elicitor bandwidth. Significant MOC-induced ΔSFOAEs were seen for a wide range of elicitor frequencies, e.g. for elicitor frequencies at least 1½ octaves away from the probe frequency for all probe frequencies. MOC-induced ΔSFOAEs were sometimes skewed so that elicitors at frequencies above (for the 0.5 kHz probe) or below (for the 1 kHz probe) the probe frequency were most effective. The largest MOC effects were for 0.5 kHz probes and the smallest for 4 kHz probes, opposite the pattern of MOC innervation, which indicates that the strength of the MOC acoustic reflex is controlled more by central factors than peripheral innervation. When MOC effect was looked at as $SFOAE_{MOC}$, the MOC-inhibited SFOAE relative to the original SFOAE, the $SFOAE_{MOC}$ magnitude decrease and phase change appeared to be separate functions of elicitor frequency. The MOC inhibition of the $SFOAE_{MOC}$ magnitude was largest for elicitors near the probe frequency whereas the MOC-induced change in $SFOAE_{MOC}$ phase was largest for off-frequency elicitors from the probe frequency. One hypothesis to account for this is that near-probe-frequency elicitors predominately inhibit the traveling wave from the probe-tone, whereas more remote off-frequency elicitors shift it along the frequency axis by selectively inhibiting apical or basal parts of the traveling-wave envelope.

VI. References

Backus, B.C. and Guinan, J. J. Jr.. (2006). 'Time-course of the human medial olivocochlear reflex,' J. Acoust. Soc. Am. 119(5 Pt 1): 2889-904.

Backus, B.C. and Guinan, J.J. Jr. (2007). 'Measurement of the distribution of Medial olivocochlear acoustic reflex strengths across normal hearing individuals via otoacoustic emissions,' J. Assoc Res. Otolaryngol. 8(4): 484-496.

Backus, B.C. (2007). 'Bias due to noise in otoacoustic emission measurements,' J Acoust Soc Am 121(3):1588-1603.

Brown, M.C. (1989). 'Morphology and response properties of single olivocochlear fibers in the guinea pig,' Hear Res. 40(1-2):93-109.

Brown, M.C., Kujawa, S.G., Duca, M.L. (1998). 'Single olivocochlear neurons in the guinea pig. I.: Bilateral facilitation of responses to high level noises,' J. Neurophys. 79(6): 3077-3087.

Chery-Croze, A., Moulin, A., Collet, L. (1993). 'Effect of contralateral sound stimulation on the distortion product 2f1-f2 in humans: Evidence of a frequency specificity,' Hear Res 68: 53-58.

Cooper, N.P. and Guinan, J.J. Jr. (2003). 'Separate mechanical processes underlie fast and slow effects of medial olivocochlear efferent activity,' J. Physiol. 548(Pt 1): 307-312.

Delgutte, B. (1990a). 'Physiological mechanisms of psychophysical masking: Observations from auditory-nerve fibers,' J. Acoust. Soc. Am. 87(2):791-809.

Delgutte, B. (1996). 'Physiological models for basic auditory percepts,' in Auditory Computation, edited by H. L. Hawkins, T..A. McMullen, A. N. Popper, and R.R. Fay (Springer, New York).

Dolan, D.F., Guo, M.H., Nuttall, A.L. (1997). 'Frequency-dependent enhancement of basilar-membrane velocity during olivocochlear bundle stimulation,' J. Acoust. Soc. Am. 102:3587-3596.

Egan, J.P. and Hake, H.W. (1950). 'On the masking pattern of a simple auditory stimulus,' J. Acoust. Soc. Am. 22:622-630.

Gifford, M. L. and J. J. Guinan, Jr. (1983). "Effects of crossed-olivocochlear-bundle stimulation on cat auditory nerve fiber responses to tones." J. Acoust. Soc. Am. **74**(1): 115-123.

Gifford, R.H., Bacon, S.P. (2000). 'Contributions of suppression and excitation to simultaneous masking: effects of signal frequency and masker-signal frequency relation,' J. Acoust. Soc. Am. 107(4): 2188-200.

Giraud, A.L., Perrin, E., Chery-Croze, S., Chays, A., Collet, L. (1995). 'Contralateral acoustic stimulation induces a phase advance in evoked otoacoustic emissions in humans,' Hear. Res. 94(1-2): 54-62.

Giraud, A.L., Collet, L., Chery-Croze, S., Magnan, J., Chays, A. (1995), 'Evidence of a medial olivocochlear involvement in contralateral suppression of otoacoustic emissions in humans,' Brain Res. 705(1-2): 15-23.

Guinan, J. J., Jr. and M. L. Gifford (1988). "Effects of electrical stimulation of efferent olivocochlear neurons on cat auditory-nerve fibers. III. Tuning curves and thresholds at CF." Hearing Res. **37**: 29-46.

Guinan J.J. Jr. (1996). 'The physiology of olivocochlear efferents,' In: Dallos P.J., Popper A.N., Fay, R.R. (eds.), The Cochlea. New York: Springer-Verlag, pp.435-502.

Guinan, J.J., Jr., Cooper, N. 2007. Medial Olivocochlear Inhibition of Basilar-Membrane Responses to Clicks: Evidence for Two Cochlear Amplifiers? (submitted).

Guinan, J.J. Jr., Backus, B.C., Lilaonitkul, W., Aharonson V. (2003). 'Medial olivocochlear efferent reflex in humans: Otoacoustic emission (OAE) measurement issues and advantages of stimulus frequency OAEs', J. Assoc Res. Otolaryngol. 4(4):521-540.

Guinan, J.J. Jr., Warr, W.B., and Norris, B.E. (1984). 'Tonotopic organization of the olivocochlear projections from lateral and medial zones of the superior olivary complex,' J. Comp. Neurol. 226: 21-27.

Kalluri, R. and C. A. Shera (2001). "Distortion-product source unmixing: a test of the two-mechanism model for DPOAE generation." J Acoust Soc Am **109**(2): 622-37.

Kawase, T., Delgutte, B., Liberman, M.C. (1993). 'Anti-masking effects of the olivocochlear reflex, II: Enhancement of auditory-nerve response to masked tones,' J. Neurophysiol. 70: 2533-2549.

Liberman, M.C. (1988). 'Response properties of cochlear efferent neurons: monaural vs. bilateral stimulation and the effects of noise,' J Neurophysiol 60:1779-1798.

Liberman, M.C., Brown, M.C. (1986). 'Physiology and anatomy of single olivocochlear neurons in cat,' Hear Res, 24:17-36

Liberman, M. C., S. Puria, et al. (1996). "The ipsilaterally evoked olivocochlear reflex causes rapid adaptation of the 2f1-f2 distortion product otoacoustic emission." J. Acoust. Soc. Am. 99 (6): 3572-3584.

Moore, B.C. and Glasberg, B.R. (1982). 'Interpreting the role of suppression in psychophysical tuning curves,' J. Acoust. Soc. Am. 72:1374-1379.

Moore, B.C. and Vickers, D.A. (1997), 'The role of spread of excitation and suppression in simultaneous masking,' J. Acoust. Soc. Am. 102(4): 2284-2290.

Oxenham, A.J. and Plack, C.J. (1998). 'Suppression and the upward spread of masking,' J. Acoust. Soc. Am. 104(6):3500-3510.

Robertson, D. 1984. Horseradish peroxidase injection of physiologically characterized afferent and efferent neurons in the guinea pig spiral ganglion. Hearing Res. 15, 113-121.

Robertson, D., Gummer, M. 1985. Physiological and morphological characterization of efferent neurons in the guinea pig cochlea. Hearing Res. 20, 63-77.

Ruggero, M.A., Robles, L., Rich, N.C. (1992). 'Two-tone suppression in the basilar membrane of the cochlea: mechanical basis of the auditory-nerve rate suppression,' J. Neurophysiol. 68(4): 1087-1099.

Ryan, S., Kemp, D.T., Hinchcliffe, R. (1991). 'The influence of contralateral acoustic stimulation on click-evoked otoacoustic emissions in humans,' Br. J. Audiol. 25(6): 391-7.

Sachs M.B. and Kiang, N.Y. (1968). 'Two-tone inhibition in auditory nerve fibers,' J. Acoust. Soc. Am. 43(5):1120-1128.

Schrott-Fischer, A., Egg, G., Kong, W.J., Renard, N., Eybalin, M. (1994). 'Immunocytochemical detection of choline acetyltransferase in the human organ or Corti,' Hear. Res. 78(2): 149-157.

Shera, C.A. and Zweig, G. (1993b). 'Noninvasive measurement of the cochlear traveling-wave ratio,' J. Acoust. Soc. Am. 93(6): 3333-3352.

Shera, C.A., Tubis, A., Talmadge, C.L. 2005. Coherent reflection in a two-dimensional cochlea: Short-wave versus long-wave scattering in the generation of reflection-source otoacoustic emissions. J Acoust Soc Am 118, 287-313.

Veuillet, E., Collet, L., Duclaux, R. (1991). 'Effect of contralateral acoustic stimulation on active cochlear micromechanical properties in human subjects: Dependence on stimulus variables,' J Neurophysiol, 65:742-735.

Wagner, W., G. Heppelmann, et al. (2007). "Olivocochlear reflex effect on human distortion product otoacoustic emissions is largest at frequencies with distinct fine structure dips." Hear Res **223**: 83-92.

Warren, E.H., and Liberman, M.C. (1989a). 'Effects of contralateral sound on auditory nerve responses. I. Contribution of cochlear efferents,' Hear Res. 37(2):89-104.

Warren, E.H., and Liberman, M.C. (1989b). 'Effects of contralateral sound on auditory nerve responses. II. Dependence on stimulus variables,' Hear Res. 37(2):105-121.

Weber, D.L. (1983). 'Do off-frequency simultaneous maskers suppress the signal?' J. Acoust. Soc. Am. 73: 887-893.

Yasin, I., Plack, C.J. (2005). 'The role of suppression in the upward spread of masking,' J. Assoc. Res. Otolaryngol. 6(4): 368-77.

Zweig, G. (1976). 'Basilar membrane motion,' Cold Spring Harb. Symp. Quant. Biol. 40:619-633.

Zweig, G. and Shera, C. A. (1995). 'The origin of periodicity in the spectrum of evoked otoacoustic emissions,' J. Acoust. Soc. Am. 98(4): 2018-2047.

Chapter 4: The Effect of Elicitor Bandwidth on Contralateral, Ipsilateral and Bilateral Medial Olivocochlear Efferent Acoustic Reflexes in Humans at Low, Medium and High Probe Frequencies

Abstract

The purpose of this study is to systematically explore the effects of medial olivocochlear (MOC) activation as a function of elicitor bandwidth, elicitor laterality and probe-frequency. Noise bands to elicit MOC activity were varied from ½ to 6.7 octaves with the level kept at 60 dB SPL. Noise bands were centered either at the probe frequency or at 2 octaves below the probe frequency. MOC effects were quantified by the elicitor-induced change in both the magnitude and phase of stimulus frequency otoacoustic emissions (SFOAEs) from 40 dB SPL tones. Results show that the magnitude of the elicitor-induced change in the SFOAE, ΔSFOAE magnitude, increased with elicitor bandwidth both when the elicitors were centered at the probe frequency and when centered two octaves below. Elicitor-induced effects on the SFOAE vector included a decrease in magnitude and a phase advance. Both changes to the SFOAE vector usually became more pronounced with increased elicitor bandwidth. For all probes regions, broadband elicitors (0.1-10 kHz) usually gave rise to the largest MOC effect. In another experiment, the MOC effects from increasing elicitor bandwidths were calculated from measurements of the MOC effects from half-octave bands of noise at various frequencies. For contralateral elicitors, the results closely predicted the growth of MOC effect with bandwidth found in the first experiment, but for ipsilateral and bilateral elicitors they consistently overestimated it. This indicates that for contralateral elicitors there was little, if any, interaction between the effects of the noise bands during their spatial summation to produce the effects found with wide-band elicitors, but for ipsilateral and bilateral elicitors, something else must be happening. Overall, the results indicate that, since the energy-level of the elicitors were kept constant, the spatial summation produced by recruiting MOC activity over elicitor frequency regions remote from the probe frequency was greater than the effect of reducing the spectral level of the elicitor near the probe frequency. Our results reveal that efferents from over almost the entire cochlear length can collectively affect the mechanical response at a specific cochlear place.

Abbreviations

ANOVA	Analysis of Variance	**NBN**	Half-Octave Narrow Noise-Band
BBN	Broadband Noise	**SFOAE**	Stimulus Frequency Otoacoustic Emission
BM	Basilar Membrane	**$\mathbf{SFOAE_{MOC}}$**	Remaining SFOAE vector from MOC-induced changes
EOAE	Evoked Otoacoustic Emission	**SNR**	Signal-to-Noise Ratio
MEM	Middle-Ear Muscle	**STD**	Standard Deviation
MOC	Medial Olivocochlear	**ΔSFOAE**	Complex change in the SFOAE (MOC Effect)

I. Introduction

Medial olivocochlear (MOC) efferents provide gain control to the cochlear amplifier by altering the properties of the outer hair-cells (OHCs) (for a review, see Guinan, 1996). OHCs are thought to be the active elements responsible for cochlear amplification. Electrical stimulation of the efferent system has been shown to reduce the mechanical response of the basilar membrane (BM) (e.g. Cooper and Guinan, 2003), but it can increase the response to a brief stimulus in a noisy background an effect called "unmasking" (Kawase et al., 1993). Such MOC-induced "unmasking" is thought to be one of the main benefits to hearing provided by MOC efferents. Our understanding of this unmasking, and of other effects produced by MOC efferents are limited by insufficient understanding of the relationship between the properties of the acoustic stimulus and MOC activation. This study is directed at filling in knowledge of how MOC activation varies with elicitor stimulus bandwidth.

Previous studies have shown that the bandwidth of the sound that elicits MOC activity can significantly affect the amount of MOC activity. Chapters 2 and 3 of this thesis showed that, in humans, narrow-band noise elicitors can evoke more efferent activity than their tonal counterparts. Maison et al. (2000) reported that, in humans, for probe frequencies of 1 and 2 kHz, efferent-induced changes in the evoked otoacoustic emission increased with increasing bandwidth of contralateral elicitors up to 2 octaves, the widest noise bands tested. But in Chapters 2 and 3 of this thesis, significant contralateral MOC effects were found over a span of 5 octaves around a probe-frequency region in some individuals. Hence, it appears that the true extent of MOC bandwidth summation could be wider than the 2-octave limit of the previous human study. Moreover, as the study by Maison et al. (2000) used only contralateral elicitors of MOC activity, the dependence of the MOC effects on ipsilateral and bilateral elicitor bandwidth remains unexplored.

In this study, we measured MOC effect as a function of elicitor bandwidth for contralateral, ipsilateral and bilateral elicitors, using SFOAEs from probe tones at frequencies near 0.5, 1 and 4 kHz. The elicitor noise bands were either centered at, or two-octaves below, the probe frequency. We also analyzed the MOC effects on both the magnitude and phase of the SFOAE vector. In another experiment, the MOC effects, in terms of ΔSFOAE magnitude, from increasing elicitor bandwidths were calculated by combining the MOC effects from half-octave bands of noise at various frequencies. The results show that, at all probe regions tested, the MOC effect generally increased with increasing elicitor bandwidth. The MOC effect was usually greatest for the widest elicitors, elicitors for which the spectral band covered a spectrum from 0.1 to 10 kHz. Hence, the feedback control provided by the MOC efferent system to a specific cochlear location can be induced collectively from almost the entire cochlear length.

II. Methods and Analysis

A. Subjects

All subjects included in this study had clinically normal hearing thresholds in both ears (within 20 dB re. ANSI pure tone threshold from 250 Hz to 4 kHz). Measurements were conducted in a sound-proof room. A warning light was automatically turned on before each stimulus presentation and the subject was instructed to sit still during the time that the light was on and sounds were presented. Subjects were rejected from the study if 1) the subject's middle-ear muscle (MEM) contractions were significant at the stimulus levels used for the experiments (See MEM-test in section D), 2) the subject was unable to remain awake and sit still during the experiment, or 3) the subject did not return to complete the study. A minimum SNR criterion of 3 (~9.5 dB) was applied to each data set to minimize amplitude estimation bias resulting from low SNR (Backus, 2007). This minimum SNR criterion was set to avoid significant amplitude estimation biases resulting from low SNR (Backus, 2007). The 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. The number of ears and subjects involved in this study are summarized in table 1.

Probe Frequency Region	Experiment Type	Subjects Included		Number of Ears included in Study	Subject Age Range (Years)	Average Subject Age (Years)
		Male	Female			
0.5 kHz	BW	1	2	5	22-35	27
1.0 kHz	BW	4	4	15	21-30	25.3
	OCBW	2	3	6	21-25	23.2
	Swept-NBN	3	3	12	21-30	24.7
	Swept-NBN Level Series	1	2		24-30	26.3
4.0 kHz	BW	1	4	9	21-42	25.6
	OCBW	0	3	3	22-35	27

Table 1: Summary of subject gender, subject age and the number of subjects included in the study. BW refers to the elicitor bandwidth experiment in which the noise bands were centered at the probe. OCBW refers to the off-centered bandwidth experiment where the noise bands were centered at 2 octaves below the probe frequency.

B. Acoustic Stimuli

As a probe sound to evoke SFOAEs in both ears, a 40-dB SPL continuous tone[16] selected at a frequency within ±10% of 0.5, 1 or 4 kHz was presented bilaterally through the earphones of 2 Etymotic ER10C acoustic assemblies. For each subject, a probe frequency was selected that: (1) was at least 100 Hz away from any spontaneous OAE with magnitude above -10 dB SPL (this was done to avoid possible entrainment – van Dijk, et al., 1988), and (2) produced the largest ΔSFOAE magnitude to a 60 dB SPL, contralateral broad-band noise (so that the signal/noise ratio (SNR) criteria could be reached with the smallest number of stimulus repeats).

To elicit MOC activity, a 60 dB SPL noise band was presented ipsilaterally, contralaterally or bilaterally for 2.5 s. Preceding the elicitor was a 0.5 s onset period from which the baseline response was measured, and following the elicitor was a 2 s period for recovery. The resulting stimulus repetition period was 5 s (Fig. 1A). Three types of experiments were done. Details of these experiments can be found in sections B1, B2 and B3. In each experiment elicitors were presented in a randomized order to avoid bias.

The baseline SFOAE (the SFOAE preceding the MOC elicitor) was measured from the vectorial difference of the ear-canal sound pressure from the 40 dB SPL probe tone with and without a 60 dB SPL suppressor tone at 110 Hz below the probe frequency[17]. The baseline SFOAE vector was measured

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[16] Contralateral tones at the probe frequency presented at 40 dB SPL were found to be weak elicitors of efferent response (Guinan et al., 2003).

[17] Backus and Guinan (2007) found that the SFOAE obtained using these parameter values can underestimate the true SFOAE amplitude, i.e. the suppressor produces only 80-100% suppression. The variability in the *degree* of

separately from the induced-change in SFOAE in runs in which the suppressor was presented for 0.5 s every 1 s (Fig. 1B). For both suppressor-tones and MOC-elicitors, 5-ms rise/fall cosine ramps were introduced at the presentation edges to minimize spectral splatter. Consecutive elicitor or suppressor presentations had opposite polarities so that upon averaging their acoustic waveforms would cancel leaving a residual measure equal to the amount of induced change in the SFOAE vector.

Calibrations of the acoustic output from the two sound sources in each ER10C acoustic assembly were done (using the microphone in the ER10C) at the beginning of every data gathering session and frequently within a session. Noise bursts were made to be spectrally flat by applying these calibrations.

B1. Experiment 1: Elicitor Noise Bandwidth Series (BW)

In the first experiment, MOC effects were measured as a function of elicitor noise bandwidth with the noise bands centered (on a logarithmic scale) at the probe frequency. For 0.5 and 1 kHz probes the noise bandwidths were 0.5, 1 ,2 and 4 octaves, and for the 4 kHz probe the noise bandwidths were 0.5, 1, 2 octaves. In addition, for all probe frequencies, broadband noise (BBN) (0.1 - 10 kHz) was presented and became the widest elicitor band. Since the BBN stimulus was not centered on the probe frequencies of 0.5 and 4 kHz, in the figures BBN points are shown connected to the other points with dashed lines. The bandwidth series and the BBN stimulus were different data sets so the SNR criterion that the maximum point must have a SNR > 3 (~9.5 dB) was applied to each separately.

B2. Experiment 2: Off-Centered Elicitor Noise Bandwidth Series (OCBW)

In the second experiment, MOC effects were measured as a function of elicitor noise bandwidth with the noise bands centered (on a logarithmic scale) two octaves below the probe frequency. This was done to determine if the increase in MOC effect with increasing noise bandwidth depended on the noise band being centered on the probe tone. In this experiment, noise bands with bandwidths of 0.5, 1, 1.5 and 2 octaves were used, and data were obtained only for 1 and 4 kHz probes. One advantage of these off-centered noise bands is that they did not have frequency components near the probe frequency and did not produce significant two-tone suppression (see Appendix). Thus we were able to measure the MOC effects in a window during the elicitor (see below).

B3. Experiment 3: Combining MOC effects from half-octave noise elicitors to obtain MOC effect (ΔSFOAE magnitudes) as a function of noise bandwidth

In the third experiment, the MOC effects, in terms of ΔSFOAE magnitudes, as a function of elicitor-noise bandwidth were calculated from measurements of the ΔSFOAEs from half-octave bands of noise at various frequencies. This task was complicated by the fact that as the noise bandwidth increased, its spectral level decreased (to keep the overall level at 60 dB SPL). To do the calculation, two sets of measurements were required: (1) Measurements of ΔSFOAEs as a function of elicitor frequency for half-octave, narrow-band noise elicitors, and (2) Measurements of MOC-effect (ΔSFOAE magnitude) growth as a function of elicitor level for these half-octave bands (how these were combined is explained below in Section E). ΔSFOAE as a function of elicitor center frequency was measured in 12 ears (6 subjects) with half octave bands of noise presented in half-octave steps from 2 octaves below to 2 octaves above the probe frequency. To construct MOC-effect growth functions, the elicitor frequency sweeps were done at 30, 45 and 60 dB SPL. Obtaining each set of these data required many hours of subject measurement

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underestimation could have increased the standard error of our group averages. However, underestimation of the SFOAE magnitude did not affect the shape of the MOC effect curves because, for a given ear, all points were normalized by the same SFOAE measure.

time and this was only done on 3 ears (3 subjects[18]). For each half-octave noise band and each sound level, the magnitudes of the ΔSFOAEs measured in the 3 ears were averaged. The resulting ΔSFOAE magnitudes as functions of elicitor level constitute the growth functions that were applied to each of the frequency functions from the previous step.

C. Measurement Analysis

Responses were rejected as being contaminated with artifacts when the difference between one pair of responses and the next pair exceeded a criterion. Stimulus pairs were used because elicitors (or suppressors) were alternated in polarity across stimulus repetitions. Multiple response pairs were vectorially averaged to achieve response averages with $N \geq 12$ stimulus repetitions. The averaged waveforms were then heterodyned to obtain the complex waveform of the response at the probe frequency. Details of the heterodyning method and specification of the frequency domain filtering can be found elsewhere (Guinan et al, 2003).

The complex amplitude of the ear canal sound pressure at the probe frequency, P(t), is the sum of the probe-tone and the evoked SFOAE(t) complex amplitude. An MOC elicitor, or a suppressor, can induce a change in the SFOAE and thereby change P(t). Changes in the SFOAE(t), ΔSFOAE(t), were calculated from P(t) by the vectorial difference between P(t) and P_{baseline} where P_{baseline} is the vector average of P(t) between 50-450 ms, i.e. the average P(t) before the onset of the suppressor or MOC elicitor (see Guinan 2003 for more detail). The MOC-induced change was then expressed as a fraction of the SFOAE by dividing ΔSFOAE(t) by the baseline SFOAE vector. That is,

$$\Delta\text{SFOAEn}(t) = \frac{P(t) - P_{\text{Baseline}}}{\text{SFOAE}} = \frac{\Delta\text{SFOAE}}{\text{SFOAE}} \qquad \text{(eq. 1)}$$

where,

$P(t)$ = the complex heterodyned measurement, and $0 < t < 5$s.
P_{Baseline} = the vectorial average of P(t), and $0.05 < t < 0.45$s
SFOAE = the complex baseline stimulus frequency otoacoustic emission evoked by the probe tone.
ΔSFOAEn(t) = the change in the SFOAE normalized by the baseline SFOAE.

In the equation above, SFOAE(t) and ΔSFOAE(t) were the raw, un-normalized values and ΔSFOAEn(t) was the normalized value. In all of the remaining, we will use only the normalized values and will drop the "n" so that henceforth ΔSFOAE(t) = ΔSFOAEn(t) of above.

Normalized ΔSFOAE(t) data were vectorially averaged in either a 0.4 s "during-elicitor" time window ending 0.05 s before the end of the elicitor (for contralateral ΔSFOAE(t)), or a 0.1 s "post-elicitor" time window starting at 0.05 s after the end of the elicitor (for ipsilateral and bilateral Δ SFOAE(t) and, for comparison, contralateral ΔSFOAE(t)). Averaging in the post-elicitor window avoids two-tone-suppression effects of the probe that can be evoked by ipsilateral and bilateral elicitors, but at the expense of capturing the MOC effect during its decay. Two-tone-suppression is absent for contralateral elicitors so the contralateral ΔSFOAE(t) can be averaged from a during-elicitor window near the end of the elicitor presentation which allows us to capture the maximum MOC effect elicited. The noise floor estimate was obtained from averaging the ΔSFOAE(t) in a time-window of the same duration as the (during or post-

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[18] These subjects were the same subjects used to derive the tuning curves in chapter 2 (S179R, S181R, S216R).

elicitor) data-analysis time window, but positioned such that the end of the noise time window was 50 ms before the end of a stimulus repetition period.

The change in the SFOAE produced by MOC activity was considered in two ways. The first way, ΔSFOAE, was explained above, and is shown in Figure 2 for a fixed time point (or for the average in a response time window). The second way is as the SFOAE obtained during MOC inhibition, $\mathrm{SFOAE_{MOC}}$, also shown in Figure 2. With the two measured quantities being the SFOAE and the ΔSFOAE vectors, $\mathrm{SFOAE_{MOC}}$ was calculated as:

$$\mathrm{SFOAE_{MOC}} = \frac{\mathrm{SFOAE} - \Delta\mathrm{SFOAE}}{\mathrm{SFOAE}} = \frac{A_{\mathrm{SFOAE_{MOC}}} e^{i\theta_{\mathrm{SFOAEMOC}}}}{A_{\mathrm{SFOAE}} e^{i\theta_{\mathrm{SFOAE}}}} = \frac{A_{\mathrm{SFOAE_{MOC}}}}{A_{\mathrm{SFOAE}}} e^{i(\theta_{\mathrm{SFOAEMOC}} - \theta_{\mathrm{SFOAE}})} \qquad \text{(eq. 2)}$$

In eq. 2 above, ΔSFOAE is the value of ΔSFOAE before it was normalized by the SFOAE magnitude (throughout the rest of the text, ΔSFOAE refers to the normalized ΔSFOAE). This equation for $\mathrm{SFOAE_{MOC}}$ includes normalizing by the magnitude of the original SFOAE magnitude, and referencing the phase of $\mathrm{SFOAE_{MOC}}$ to the phase of the original SFOAE.

D. Middle-ear-muscle (MEM) contraction test

A MEM test was performed on each subject to ensure that the MEMs were not activated at the stimulus levels used. In this test, a 65 dB SPL continuous suppressor tone at 110 Hz above the probe frequency was presented in addition to the normal acoustic stimuli. With this paradigm, only MEM contractions produce a change in the sound pressure at the SFOAE probe frequency. Thus, 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 has been no significant MEM contraction. Details of the experimental rational can be found in the Methods section of Chapter 2.

E. Calculation of MOC effect as a function of elicitor bandwidth by combining the MOC effects from half-octave noise bands

The task of calculating MOC effect (|ΔSFOAE|) as a function of elicitor bandwidth by combining the MOC effects from half-octave noise bands is complicated by the fact that as the noise bandwidth increased, its spectral level decreased. We need to know the MOC effect produced by the half-octave band when presented at the same spectral level as the elicitor in the bandwidth series at the bandwidth we are trying to mimic. For each half-octave band, this was done by interpolation from the MOC effects expressed as a level series. The procedure was done in the following steps: (1) Calculate the equivalent sound level in dB SPL of a half-octave band with the same spectral level as the bandwidth-series noise to be replicated (method in Section E1). (2) Using this equivalent sound level of the half-octave band, estimate the *corresponding MOC-effect* by interpolation from the MOC-effect growth function of that half-octave band (method in Section E2.). (3) The *corresponding MOC-effects* of the half-octave bands were then vectorially added.

E1. Determination of dB SPL of NBN sub-band

The definition of dB SPL is as follows:

$$dBSPL = 10\log_{10}\left(\frac{P_{rms}^2}{P_o^2}\right) \qquad \text{(eq. 3)}$$

where,

P_o = reference sound pressure.

P_{rms} = The root-mean-squared ear canal sound pressure being measured.

For a given flat-spectrum noise band with f_2 and f_1 as its upper and lower frequency edges,

$$P_{rms} = \sqrt{\frac{(P(f_2 - f_1))^2}{(f_2 - f_1)}} = P\sqrt{(f_2 - f_1)} \qquad \text{(eq. 4)}$$

where,

P = the spectrum level.

From equations 3 and 4, we can calculate the sound level in dB SPL of a flat-spectrum noise band (frequency spectrum between f_1 and f_2) so that the spectral level is equivalent to that of another flat spectrum noise band (frequency spectrum between f_l and f_h) at x dB SPL:

$$dBSPL = 10\log_{10}\left(\frac{10^{x/10}P_o^2\left(\frac{f_h - f_l}{f_2 - f_1}\right)}{P_o^2}\right) \qquad \text{(eq. 5)}$$

where, the noise band (width f_2-f_1) was at x dB SPL, which in our case, x = 60.

E2. Use of MOC-effect growth functions

To estimate the MOC-effect that would be elicited by a half-octave NBN at a sound level equivalent to the sound level of the bandwidth-series noise to be replicated, we used a scaled value obtained from the MOC-effect growth function for the half-octave NBN. For each half-octave NBN this was done as follows:

$$G_S(L) = G_A(L) \times \frac{G_S(60)}{G_A(60)} \qquad \text{(eq. 6)}$$

where,

$G_A(L)$ = The average growth function,

$G_S(L)$ = The estimated growth function for a given subject,

L = The elicitor level (from Eq. 4),

$G_A(60)$, $G_S(60)$ = the value of these functions at 60 dB SPL.

F. Determining the statistical significance of variations across parameters

To determine the statistical significance of the variations of MOC effect 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 MOC effect results passed the Lillifores test for normality. If they did not pass, the Friedman non-parametric two-way ANOVA was used. Statistical significance was accepted at the 0.05 level. The data were compared to a control data set that measured the response under the Null-hypothesis of no MOC effect. The control data were the noise floor measurements taken from a time-window of the same duration as the (during or post-elicitor) data-analysis time window, but positioned such that the end of the noise time window was 50 ms before the end of a stimulus repetition period.

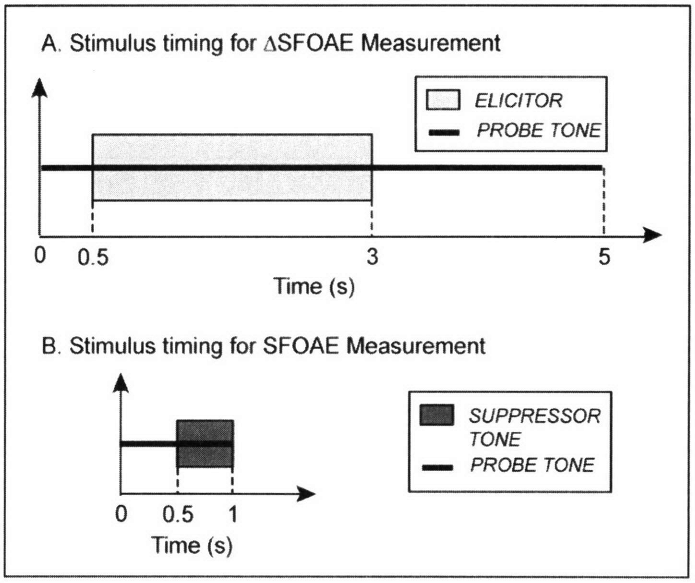

Figure 1. Temporal presentation of stimuli. A. For the measurement of the elicitor-induced ΔSFOAE, there was an initial delay of 0.5 s to establish the baseline response, then a 2.5 s tone or noise burst to elicit MOC activity, followed by a 2 s recovery period. This stimulus pattern was repeated every 5 s with the polarity of the elicitor alternated so that upon averaging the measurements, the elicitors would cancel leaving a residual pressure equal to elicitor-induced ΔSFOAE. **B**. For the SFOAE measurement, there was an initial delay of 0.5 s to establish the baseline response, then a 0.5 s suppressor tone at 110 Hz below the probe frequency. This stimulus pattern was repeated every 1 s with the polarity of the suppressor alternated.

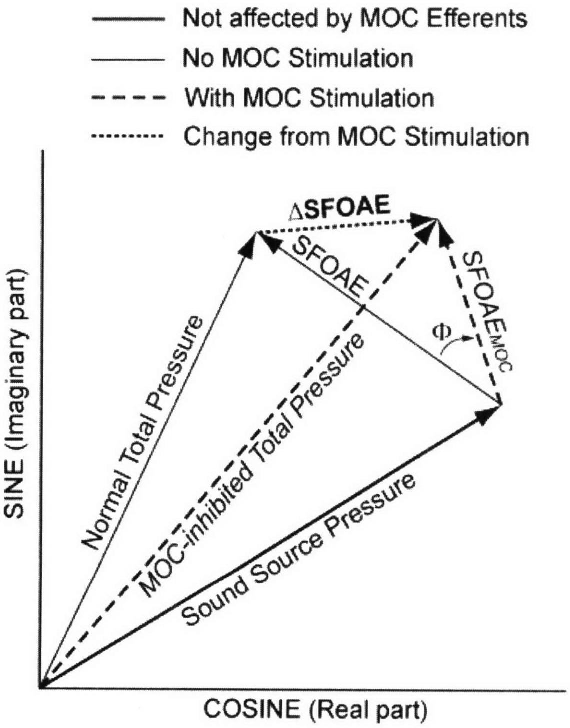

Figure 2. Vector diagram of MOC-elicitor effects on sound pressures in the ear canal. The arrows are vectors in the complex plane such that the length of the arrow represents the magnitude and the direction of the arrow represents the phase. Before stimulation by the MOC-elicitor, the *Sound Source Pressure* and the SFOAE summate to form the *Normal Total Pressure* in the ear canal. In the presence of an MOC-elicitor the SFOAE magnitude and phase are changed as shown by $\text{SFOAE}_{\text{MOC}}$ resulting in a new ear-canal sound pressure (*MOC-inhibited Total Pressure*). The change in the ear canal pressure shows the resulting change in the SFOAE, ΔSFOAE. Note that the angle ϕ shows the phase delay of $\text{SFOAE}_{\text{MOC}}$ from the SFOAE phase, opposite the sign convention used in the other figures.

III. Results

In the first part of this study, we measured MOC effects as a function of elicitor bandwidth at probe frequencies of 0.5, 1 and 4 kHz, by systematically varying the bandwidths of noise-band elicitors centered at the probe frequencies or 2 octaves below the probe frequencies (Results Sections A and B). MOC effects were analyzed in two ways: (1) as the magnitude of the elicitor-induced change in the SFOAE ($|\Delta$SFOAE$|$) and 2) the MOC-inhibited SFOAE vector, SFOAE$_{MOC}$ (Fig. 2). Both were normalized so that they are expressed as a fraction of the original SFOAE (see Methods). Some interesting features of these results are further analyzed in Results Sections C and D. Finally, Results Section E presents the MOC effect (ΔSFOAE magnitude) as a function of elicitor bandwidth calculated from measurements of the ΔSFOAEs from half-octave bands of noise. For all of these experiments, MEM-tests revealed no significant MEM contractions in response to the stimulus levels used in this study. Hence, all of the measured elicitor-induced changes arose from within the cochlea, presumably due to MOC activity.

A. MOC effects for bandwidth series centered at the probe frequency

To investigate MOC effects as a function of elicitor bandwidth at probe frequencies of 0.5, 1 and 4 kHz, we quantified the effects by (1) the magnitude of the MOC induced-change in the SFOAE (ΔSFOAE) and (2) the magnitude and phase of the resulting SFOAE (SFOAE$_{MOC}$) (see Fig. 2). No significant differences were found between the average left and right ear responses so the data were pooled. Magnitudes of ΔSFOAE as functions of elicitor bandwidth centered at the probe frequency are shown in Figure 3 (top row). Elicitor bandwidth and laterality, as well as inter-subject differences, all produced significant variation of ΔSFOAE magnitudes at each probe frequency (ANOVA results in Table 2). For all probe frequencies and elicitor lateralities, the magnitude of ΔSFOAE increased as the elicitor bandwidth increased, with some evidence that the value reached a plateau at the widest bandwidth (Fig. 3, top row). The increase in response was observed despite the fact that the noise energy in a frequency band around the probe frequency decreased as bandwidth increased because the overall elicitor level was held constant. Figure 3 (top) also shows that for all probe frequencies, the bilateral response magnitude was generally greater than the ipsilateral and contralateral response regardless of the elicitor bandwidth. Moreover, ipsilateral ΔSFOAE magnitude was greater than the contralateral ΔSFOAE magnitude when elicitors were narrow (looking only at data from the post-elicitor window where ipsilateral data in red and contralateral data in blue were measured in the same way). However, as elicitor bandwidth increased, the ΔSFOAE magnitude from ipsilateral and contralateral elicitors eventually converged.

The magnitudes and phases of SFOAE$_{MOC}$ as functions of elicitor bandwidth are shown in the middle and bottom rows of Figure 3, respectively. MOC effects as shown by the SFOAE$_{MOC}$ include magnitude inhibition and phase advances. For all probe frequencies and elicitor lateralities, elicitor bandwidth had significant effects on the inhibition of SFOAE$_{MOC}$ magnitude. In general for all elicitor bandwidths, bilateral elicitors produced greater magnitude inhibition than ipsilateral or contralateral elicitors. For 0.5 and 1 kHz, magnitude inhibitions from bilateral elicitors could be over 40% (so that the SFOAE$_{MOC}$ magnitude was less than 60%), while the largest magnitude inhibition at 4 kHz was ~10%. MOC activity also produced a phase advance of the SFOAE$_{MOC}$. In general, for all lateralities and probe frequencies, the phase advance increased with increasing elicitor bandwidth. The greatest phase leads were elicited by bilateral elicitors. Ipsilaterally elicited phase leads and contralateral phase leads near 0.5 and 4 kHz were not statistically different for all elicitor bandwidths. At 1 kHz, contralateral elicitors elicited greater phase leads than ipsilateral elicitors for narrow noise bands (2 octaves or less). However, this phase difference decreased as bandwidth increased so that with BBN the phase leads from ipsilateral and contralateral elicitors became approximately equal. The maximum phase lead at each probe frequency was elicited by wide-band bilateral elicitors and was > 25 degrees at 0.5 kHz, > 30 degrees at 1 kHz and ~10 degrees at 4 kHz.

B. MOC effects for bandwidth series centered two octaves below the probe frequency

To determine if the changes in MOC effect with bandwidth was only true for elicitors centered at the probe frequency, we did bandwidth series with the elicitor centered two octaves below the probe frequency. Figure 4 shows the MOC effect as a function of elicitor bandwidth when the elicitors were centered two octaves below the probe frequencies. Similar to the results observed with probe-centered noise bands, the off-centered noise bands elicited increasing MOC effects (as measured by the magnitude of ΔSFOAE) with increasing elicitor bandwidths for all elicitor lateralities and probe frequencies (Fig. 4 top row). Magnitude inhibition and phase advance as shown by $\mathrm{SFOAE_{MOC}}$ were also observed with off-centered noise bands (Fig. 4 middle and bottom rows, respectively). Near 1 kHz only ipsilateral elicitors with wide bandwidths (1.5 and 2 octaves) elicited significant $\mathrm{SFOAE_{MOC}}$ magnitude inhibition while near 4 kHz both ipsilateral and bilateral elicitors of bandwidths greater than 1 octave were able to elicit significant $\mathrm{SFOAE_{MOC}}$ magnitude inhibition. Unlike the results for probe-centered elicitors where a significantly greater MOC effect was observed near 1 kHz than near 4 kHz (Fig. 3, middle row), the amount of $\mathrm{SFOAE_{MOC}}$ magnitude inhibition elicited by off-centered noise bands were not statistically different for 1 kHz versus 4 kHz probes (Fig. 4, middle row). The maximum inhibition by off-centered noise bands (measured in the during-elicitor window) was between 5-10%, which is much less than that found with on-center elicitors (measured in the post-elicitor window). All off-centered elicitor lateralities elicited significant phase leads in $\mathrm{SFOAE_{MOC}}$ and the phase lead increased with increasing elicitor bandwidth. The phase lead as a function elicitor bandwidth was remarkably similar for the two probe frequencies. Greater phase leads were elicited with bilateral elicitors while approximately equal phase leads were elicited by the ipsilateral and contralateral elicitors. The maximum phase lead was elicited by the two-octave, bilateral elicitor which introduced a phase lead of approximately 10 degrees for both probe frequencies.

C. Rate of growth of MOC effects as functions of probe frequency and elicitor laterality.

As noted above, ΔSFOAE magnitudes grew as bandwidth increased, however, the data of Figures 3 and 4 indicate that the pattern of this growth may be different depending on whether the elicitor was centered on the probe frequency, or not. To better view the patterns involved, the growth of MOC effect with increases in elicitor bandwidth were calculated from the data of Figures 3 and 4 by making a linear, least-square fit to the ΔSFOAE magnitude data for elicitor bandwidths between 0.5 and 2 octaves. For each subject, the rates of growth were taken as the slopes of the linear fits to the data from each elicitor laterality and probe frequency. Then, for each elicitor laterality and probe frequency, the slopes were averaged across subjects. The results are shown in Figure 5.

For the probe-centered noise (Fig. 5A), bilateral noise bands elicited the fastest MOC-effect growth rate followed by the contralateral and then the ipsilateral noise bands. Note also that although the ipsilateral ΔSFOAE magnitude was generally larger than the contralateral ΔSFOAE magnitude (Fig. 3), the rate of MOC effect buildup as bandwidth increased was larger for contralateral than for ipsilateral elicitors (Fig. 5A). The growth of the ipsilateral and contralateral MOC effects were approximately 0.2 and 0.5 of the bilateral growth-rate, respectively. In contrast, the off-centered noise bands (Fig. 5B) showed MOC-effect growth rates that were approximately equal for ipsilateral and contralateral elicitors, and were about half the growth rate of the bilateral MOC effects. The pattern of data in Fig. 5 indicate that the ratio of ipsilateral / contralateral MOC effects is different for elicitor bandwidth centered on the probe frequency versus those two octaves below the probe frequency.

D. Strength of MOC effects as a function of probe frequency

To compare the relative strength of MOC effects across probe frequencies, the ΔSFOAE magnitudes elicited by the highest levels of the probe-centered elicitor bandwidths (from Fig. 3 top row) and the off-centered elicitor bandwidths (from Fig. 4 top row) were plotted against probe frequency in Figure 6. For the probe-centered elicitor bandwidths and half-octave noise-band elicitors, MOC effect decreased as a function of probe frequency, for all elicitor lateralities (Fig. 6, top row). However, as the elicitor bandwidth increased, the trend of decreasing MOC-effects with increasing probe frequency gradually diminished such that with BBN elicitors (Fig. 6C) the MOC effects showed little trend with changes in probe frequencies. For the off-centered elicitor bandwidths, the MOC effects were not significantly different for the 1 kHz and 4 kHz probes (Fig. 6, bottom row). For both the probe-centered and off-centered data, the bilateral MOC-effect was usually greater than either the ipsilateral and contralateral MOC-effect. Most interestingly, the ipsilateral MOC-effect was greater than the contralateral MOC-effect only for half-octave noise bands centered at the probe frequencies (Fig. 6A).

E. MOC-effect vs. bandwidth estimated from half-octave-elicitor MOC effects

To investigate if there are significant interactions during the spatial summation of elicitor sub-bands within a wider noise band in producing MOC effects, we calculated the effect of increasing elicitor bandwidth from measurements of the MOC effects from half-octave noise bands at various frequencies. This was done in several steps (see Methods E). The MOC effects, in terms of ΔSFOAE magnitudes, from half-octave noise-band elicitors with different center frequencies near 1 kHz are shown in Figure 7 (12 ears from 6 subjects). These data are similar to data shown Chapters 2 and 3, but were independently obtained from a subset of the subject pool used in making Figure 3. The MOC-effects of Figure 7 were scaled using the MOC-effect growth function (3 ears from 3 subjects) shown in Figure 8 (See E in Methods). The results were then vectorially added to give the calculated MOC effects as functions of elicitor bandwidth shown in Figure 9A. The actual measured values are shown in Fig. 9B. The same subjects were used for making Figures 9A and 9B. The calculated MOC effect as a function of elicitor bandwidth (Fig. 9A) was qualitatively similar to actual MOC effects measured (Fig. 9B). The bottom row of Figure 9 overlays the results in Figures 9A and 9B for the different elicitor lateralities. For the MOC effect versus elicitor bandwidth from contralateral elicitors, the estimated MOC effect was remarkably similar to the actual MOC effect such that the two curves overlay almost exactly (Fig. 9E). However, for the ipsilateral and binaural MOC effects, the estimated effects were generally greater than the actual MOC effects. The departure of the ipsilateral and binaural estimated MOC effects from the actual MOC effects was especially pronounced for wider noise-bands. Given the close fit achieved in the contralateral case, this departure observed for the ipsilateral and binaural effects seems likely to be due to a real physiological phenomenon rather than an estimation bias due to noise.

Probe Freq.	Elicitor Type	Bandwidth Effects	Laterality Effects	Subject Variation	Ear Orientation (Left vs. Right)
~0.5 kHz	BW	**0.02**	**$<10^{-3}$**	**0.03**	0.49
~0.5 kHz	OCBW	-	-	-	-
~1.0 kHz	BW	**$<10^{-3}$**	**$<10^{-3}$**	**$<10^{-3}$**	0.13
~1.0 kHz	OCBW	**$<10^{-3}$**	**$<10^{-3}$**	**1.10×10^{-3}**	**$<10^{-3}$**
~4.0 kHz	BW	**$<10^{-3}$**	**$<10^{-3}$**	**$<10^{-3}$**	0.36
~4.0 kHz	OCBW	**$<10^{-3}$**	**$<10^{-3}$**	**0.01**	0.94

Table 2: Summary of multi-dimensional ANOVA on ΔSFOAE magnitude to determine the effects of elicitor bandwidth, elicitor laterality, subject variation, and ear orientation (left to right). Probe-centered elicitor data (BW) data are shown in Figure 3 (top). Off-center elicitor data (OCBW) data are shown data in Figure 4 (top). Significance was taken at the 0.05 level (numbers shown in bold).

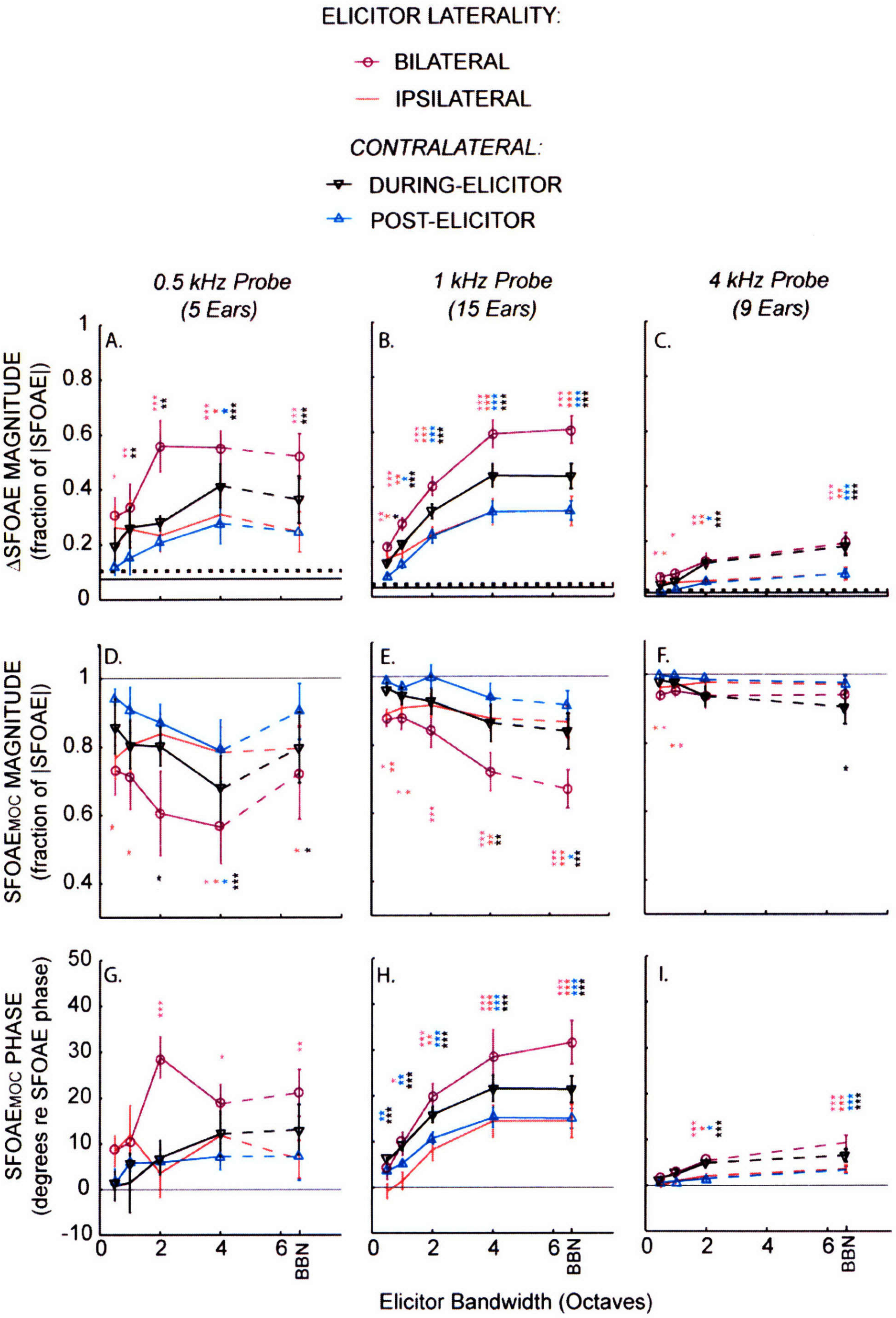

Figure 3. MOC effects as shown by ΔSFOAE magnitude (1st Row) and the resulting $SFOAE_{MOC}$ magnitudes (2nd Row) and phases (3rd Row) as functions of elicitor bandwidths centered at the probe frequency. Effects to bilateral (purple: O), ipsilateral (red: —) and contralateral (blue: Δ) 60 dB SPL elicitors were measured in the post-elicitor window. Responses to the same contralateral elicitors except measured in the during-elicitor window are also shown (black: ∇). Error bars are standard errors of the mean. Horizontal lines: Solid = noise-floor mean, dashed = 1 std. above the noise mean. Significant differences from the noise floor are marked with asterisks: '*' ($P \leq 0.05$), '**' ($P \leq 0.01$), '***' ($P \leq 0.001$).

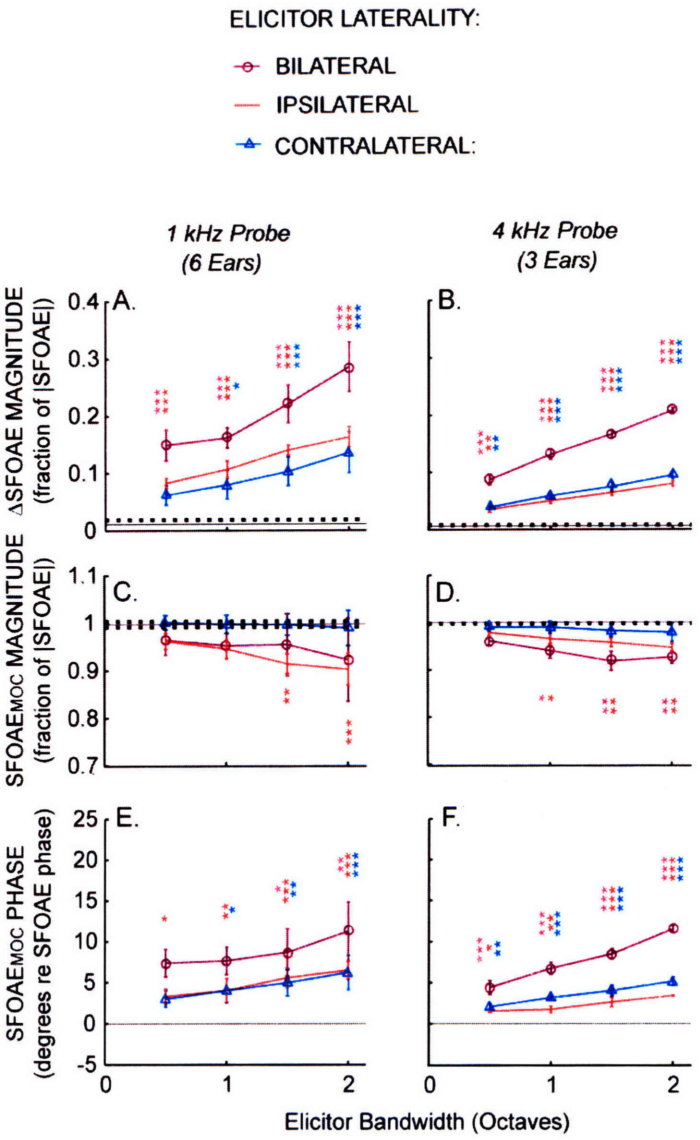

Figure 4. MOC effects as shown by ΔSFOAE magnitude (1st Row) and the resulting $\text{SFOAE}_{\text{MOC}}$ magnitudes (2nd Row) and phases (3rd Row) as functions of elicitor bandwidths centered at 2 octaves below the probe frequency. Effects to bilateral (purple: O), ipsilateral (red: —) and contralateral (blue: Δ) 60 dB SPL elicitors were measured in the during-elicitor window. Error bars are standard errors of the mean. Horizontal lines: Solid = noise-floor mean, dashed = 1 std. above the noise mean. Significant differences from the noise floor are marked with asterisks: '*' ($P \leq 0.05$), '**' ($P \leq 0.01$), '***' ($P \leq 0.001$).

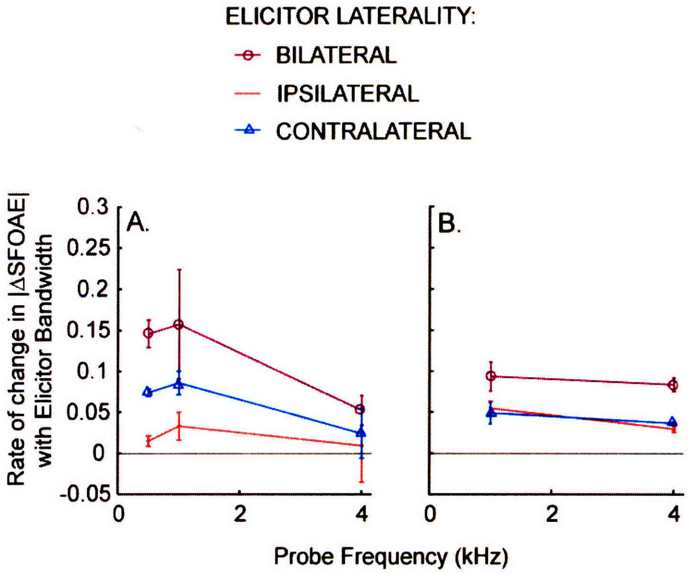

Figure 5. Rate of growth in MOC effects in terms of ΔSFOAE magnitude with elicitor bandwidth for various probe frequencies. Noise-bands were centered at the probe (A) or at 2 octaves below the probe (B). Averaging of the MOC effects were from the post-elicitor window in (A) or from the during-elicitor in (B). The growth rate was the slope of a linear-least-square-fit of a straight line to the MOC effects elicited by noisebands with bandwidths between 0.5 and 2 octaves (from data shown in the first row of Figs. 4 and 5). Error bars represent 1 standard error of the mean.

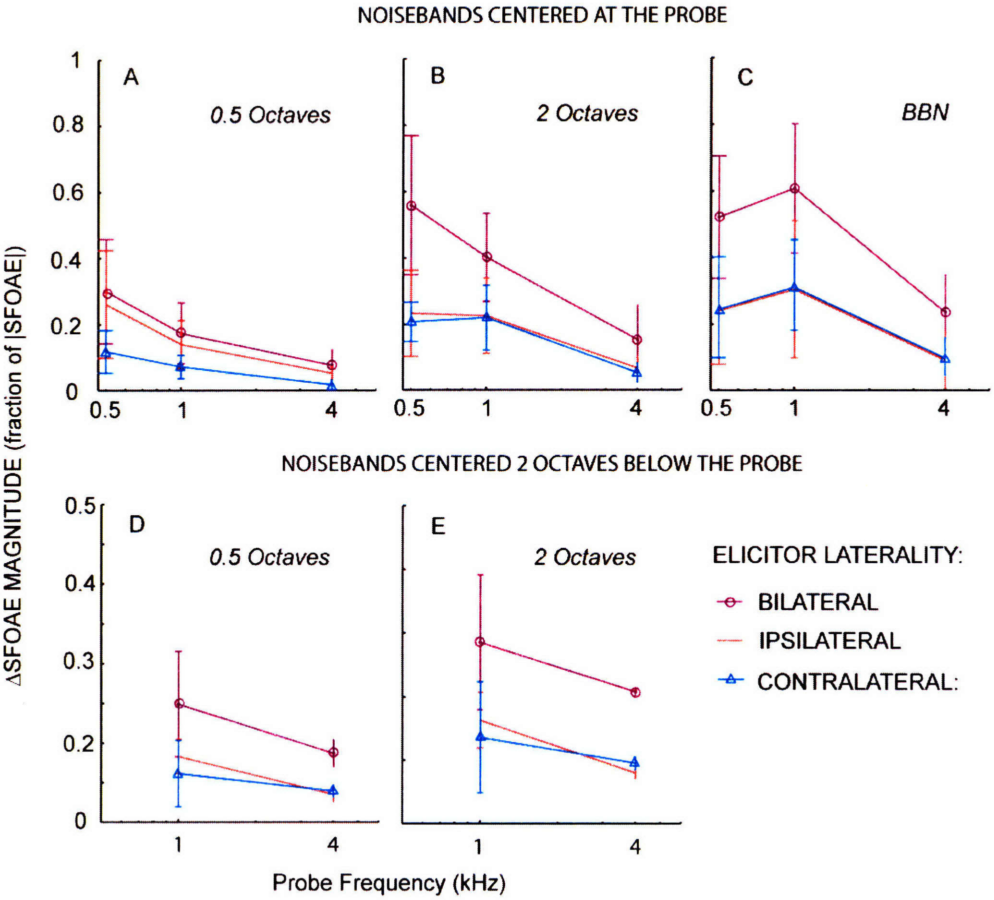

Figure 6. ΔSFOAE magnitude as a function of probe frequency. MOC effects were averaged from the post-elicitor window (top row) or from the during-elicitor window (bottom row). For the probe-centered data (top row) the number of subject ears averaged at 0.5 kHz, 1 kHz and 4 kHz were 5, 15 and 9 respectively. For the off-centered data (bottom row) the number of subject ears averaged at 1 kHz and 4 kHz were 6 and 3 respectively. Error bars represent 1 standard error of the mean.

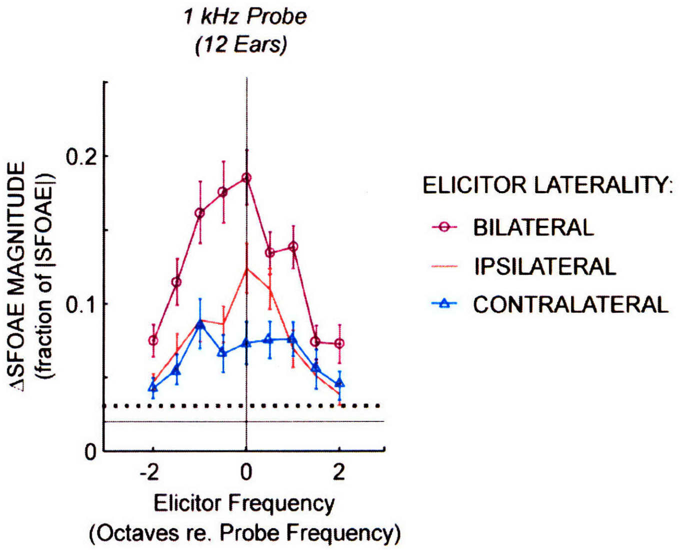

Figure 7. MOC effects in terms of ΔSFOAE magnitudes at 1 kHz from half-octave noise elicitors as functions of elicitor frequency. Elicitors were at 60 dB SPL. Data were vectorially averaged in the post-elicitor time window. Error bars represent 1 standard error of the mean. Horizontal lines: Solid = noise-floor mean, dashed = 1 std. above the noise mean.

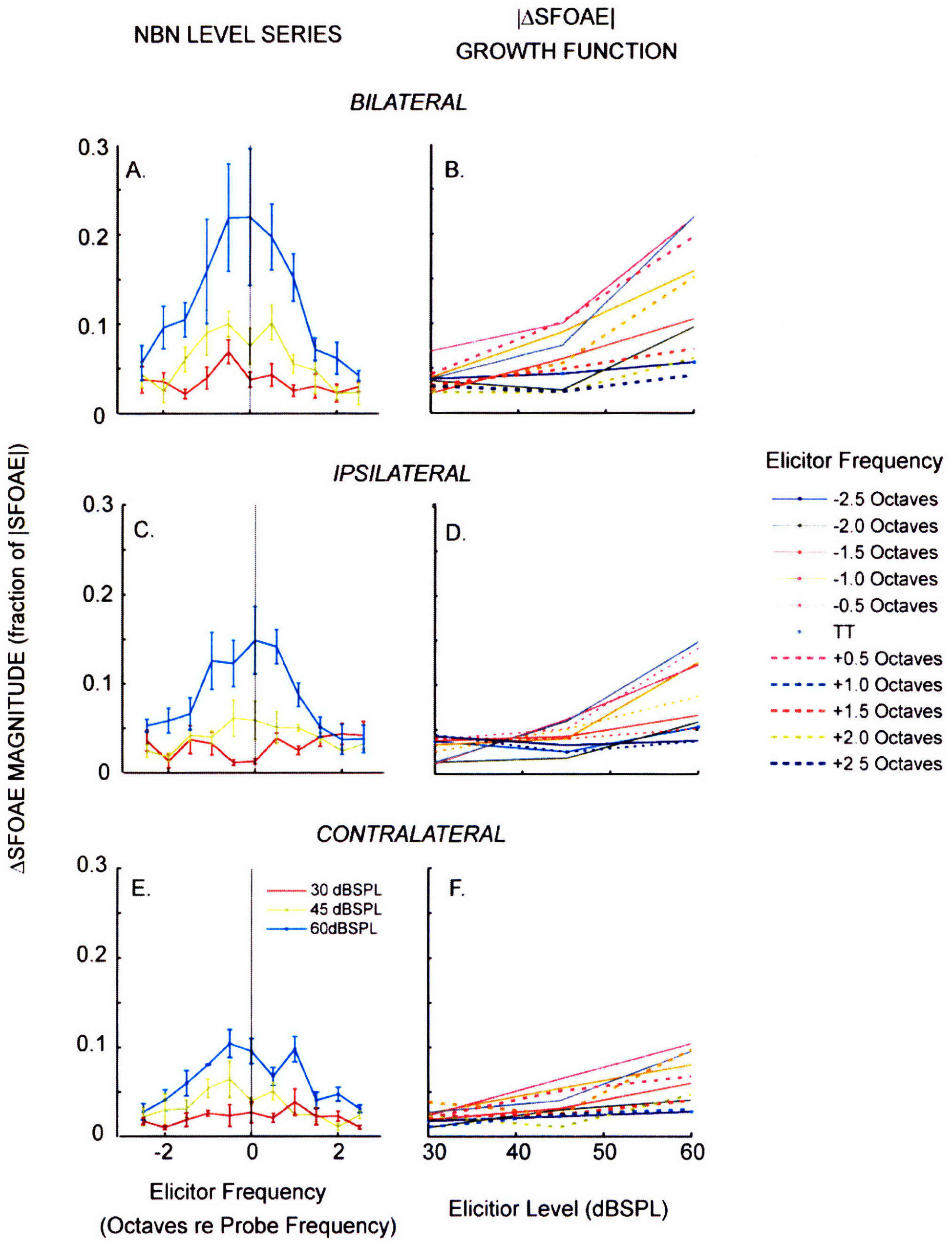

Figure 8: Left: MOC effects as functions of elicitor frequency at three sound levels. Right: MOC effect 'growth functions' derived from the data in the left column. All data are from 40 dB SPL probe tones near 1 kHz in 3 ears (3 subjects). The elicitors were bilateral, ipsilateral and contralateral to the probe ear (top to bottom). Elicitors were half-octave noise bands at 30, 45 or 60 dB SPL. Error bars (A, C, and E) represent 1 standard error of the mean.

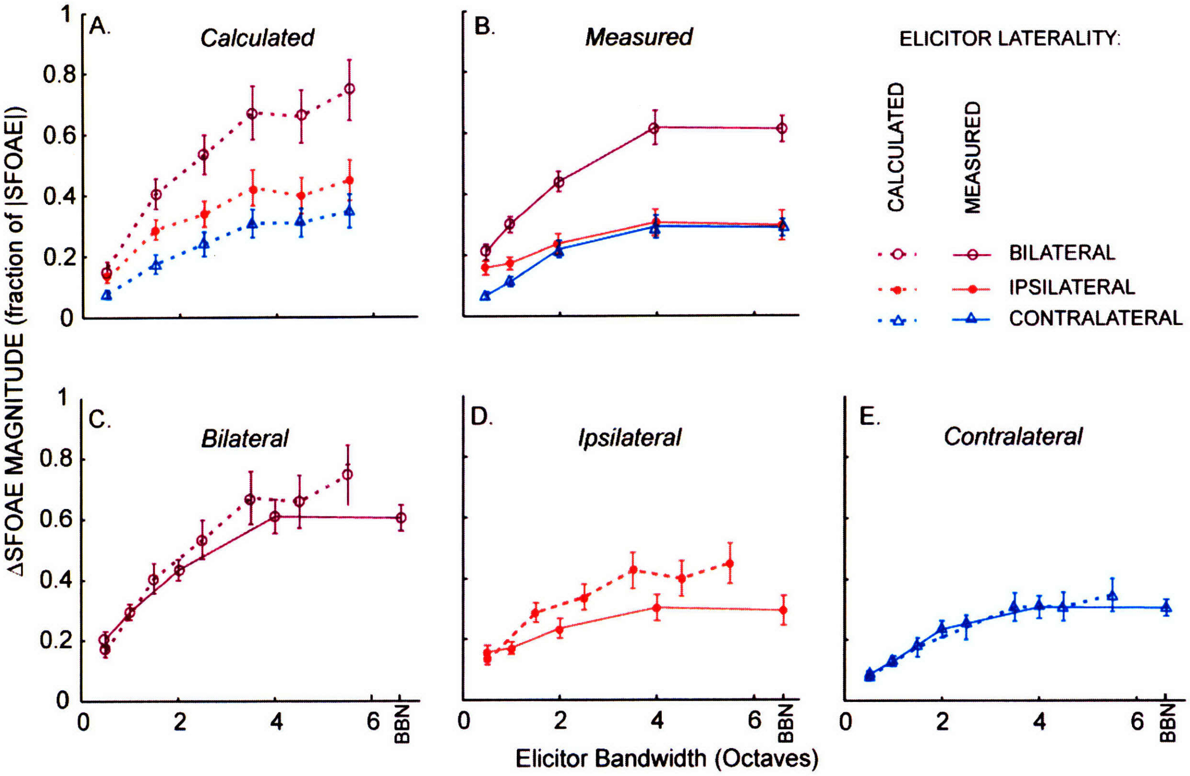

Figure 9. A comparison of the calculated MOC effects (A) to the measured MOC effects (B) as a function of elicitor bandwidth. The calculated MOC effects (A) made use of the sub-band MOC effects in Figure 7 and the growth functions of Figure 8 (See Methods). Data in both (A) and (B) were from the same 6 subjects (12 ears). For direct comparison, calculated MOC effects from A (dashed lines) and measured MOC effects from B (solid lines) are overlaid (bottom row) according to elicitor laterality. Error bars represent 1 standard error of the mean.

IV. Discussion

MOC effects increased as a function of elicitor bandwidth

Our results show that when the noise band was centered at the probe frequency, the MOC effect expressed as the magnitude of ΔSFOAE, increased with increasing elicitor bandwidths up to the widest symmetrical noise bands tested (4 octaves for 0.5 and 1 kHz probes, and 2 octaves for the 4 kHz probe). With the widest elicitor noise band, broadband noise (0.1-10 kHz), the ΔSFOAE magnitude either continued to rise or leveled off. Similar increases were found for the MOC effects produced by ipsilateral, contralateral and binaural elicitors. Hence, medial efferents that affect one frequency region of the cochlea can be activated by sounds throughout most of the cochlea. When the spectral contents of the noise bands were limited to cochlear regions apical to the probe in the off-centered bandwidth experiments, the MOC effects also increased with increasing elicitor bandwidths up to the widest noise band tested (2 octaves). So regardless of the region of activation in reference to the probe, efferent activation increased with elicitor bandwidth. Our results show that the increased output of the MOC acoustic reflex with elicitor bandwidth occurred despite the fact that the noise energy in a frequency band around the probe frequency decreased because the overall SPL was held constant as bandwidth increased. This implies that the additional frequency regions covered by increased bandwidth are adding more to the response than the loss from having lower energy near the probe frequency.

Our results are consistent with previous animal and human studies in which increased MOC reflex responses were observed with increasing elicitor bandwidth. Brown et al. (1998) reported that in guinea pigs, MOC neuron firing rates were usually higher for noise bursts than for tone bursts. Maison et al. (2000) reported that MOC effects from contralateral elicitors gradually increased with increasing bandwidth up to the maximum bandwidth tested (2 octaves). Several human psychophysical studies of "overshoot" may also be relevant. Overshoot is the phenomenon that the threshold of a simultaneously-masked signal is reduced when presented after a delay as compared to soon after the masker onset. Several investigators of overshoot have suggested that overshoot be due, at least in part, to masker inhibition produced by MOC activity evoked by the masker (e.g. Schmidt and Zwicker, 1991; von Klitzing and Kohlrausch, 1994; Turner and Doherty, 1997; Strickland, 2001) and Zeng et al. (2000) have shown some reduction in overshoot in humans whose efferent connections have been severed surgically. Several earlier psychophysical experiments on overshoot found that overshoot increased as the masker bandwidth increased (McFadden, 1981; Bacon and Smith, 1991; Zwicker, 1965b). This is consistent with the interpretation that wider-band maskers elicit more MOC activity which builds up on a 100 ms time scale, and that this MOC activity increases the audibility of the masked signal.

The MOC-induced magnitude inhibition and phase advance shown by $\mathrm{SFOAE}_{\mathrm{MOC}}$ increased with increasing elicitor bandwidth.

Both probe-centered and off-centered bandwidth experiments produced inhibition and phase advances in the SFOAE vector, as shown by $\mathrm{SFOAE}_{\mathrm{MOC}}$ (Fig. 3, middle and bottom rows). The SFOAE magnitude inhibition and phase advance elicited by bilateral elicitors were always greater than those elicited by ipsilateral or contralateral elicitors. In contrast, the relative size of the effects produced by ipsilateral versus contralateral elicitors depended on elicitor bandwidth. Although most MOC effects increased with increasing elicitor bandwidth, the ipsilateral inhibition of the SFOAE magnitude did not increase much with elicitor bandwidth: the effect of increasing elicitor bandwidth was to increase the phase advance. This is in agreement with the observations from the swept-half-octave-noise experiment of Chapter 3 where off-frequency ipsilateral elicitors were more effective at inducing a phase lead in the SFOAE vector than inducing a magnitude reduction. With elicitors centered two-octaves below the probe frequency, the SFOAE magnitude inhibition increased with increasing elicitor bandwidth, an effect not always observed with increasing bandwidths of probe-centered noise bands. This suggests that MOC effects depend somewhat differently on elicitor bandwidth for elicitors centered on the probe frequency versus those centered below the probe frequency. Moreover, the different effects induced by the ipsilateral and contralateral reflexes on the SFOAE vector may indicate that the two lateralities serve different purposes in the alteration of cochlear biomechanics.

The relative amplitudes of MOC effects produced by ipsilateral versus contralateral elicitors depend on proximity of the elicitor frequency to the probe frequency.

When MOC activation was produced by a centered half-octave noise-band, the ipsilateral MOC effect was always greater than the contralateral MOC effect (Fig. 3, top row). This is consistent with the results reported in Chapters 2 and 3 for the MOC effects produced by half-octave noise bands centered at the probe frequency. As the elicitor bandwidth increased so did the ipsilateral and contralateral MOC responses. But the growth rate of the ipsilateral MOC effect with elicitor bandwidth was lower than the growth-rate of the contralateral response (Figure 5A). The lower growth rate reflects the fact that the ipsilateral reflex strength was significantly higher than the contralateral reflex strength with narrow noise bands, but when stimulated with wide-band noise, the ipsilateral and contralateral reflex strengths become approximately equal. Approximately equal ipsilateral and contralateral MOC effects to a broadband noise elicitor (0.1-10kHz) were universal for all 3 probe regions (Fig. 3, top row & Fig. 6C). The approximately equal ipsilateral and contralateral MOC effects (ΔSFOAE magnitude) to broad-band noise around 1 kHz is consistent with results from earlier human studies where ipsilateral and contralateral MOC effects near 1 kHz were approximately equal when elicited with broad-band noise (Backus, 2005) or notched-noise (Backus and Guinan, 2006).

For off-centered elicitors, the ipsilateral and contralateral MOC effects were approximately equal for all elicitor bandwidths (Figure 4 A and B). This is consistent with the interpretation that the convergence of the two monaural MOC effects with the broadband noise is due to an increased contribution of efferent response from more remote regions where the ipsilateral and contralateral response strengths are approximately equal. Rather than the relative strengths of the ipsilateral and contralateral response being determined by a fixed relative number of efferent fibers within the cochlea, our results suggest that the relative ipsilateral versus contralateral response strengths are determined more so by central processing. It appears that the ipsilateral and contralateral MOC acoustic reflexes are more equally weighted when efferent activation is dominated by cochlear regions remote from the probe frequency.

The convergence between the ipsilateral and contralateral response to wideband elicitors was not predicted by the combined responses from half-octave elicitors (Figure 9A). In the experiment in which the MOC effects (ΔSFOAE magnitude) from increasing elicitor bandwidths were calculated from measurements of the ΔSFOAEs from half-octave bands of noise at various frequencies, the calculated and actual results were very similar for contralateral elicitors, but for ipsilateral and bilateral elicitors, the calculated results were consistently higher than the actual results (Fig. 9). Stated another way, the calculated ipsilateral MOC effects were consistently higher than the calculated contralateral MOC effects, at all elicitor bandwidths (Fig. 9A). A similar over-estimation was observed in the bilateral MOC effects. The discrepancy between the calculated ipsilateral and binaural MOC effects as function of elicitor bandwidth and the actual MOC effects measured suggests a compressive spatial summation of ipsilateral an bilateral MOC effects, but a linear summation for contralateral effects. Whether the compressive bandwidth summation arises as a result of central processing or adjustments within the periphery is unknown.

The trend of MOC effects as a decreasing function of probe frequency was observed with narrow-band elicitors but not with wide-band elicitors.

For all elicitor lateralities and probe frequencies, the largest MOC effects were usually elicited by broad-band-noise, although sometimes they were elicited by the four-octave noise band (Fig. 3). The sizes of the MOC effects were dependent on probe-frequency such that the MOC reflex effects by broad-band noise were approximately equal for the 0.5 and 1 kHz probes and much smaller for the 4 kHz probe (Fig. 6C). Our results are consistent with a previous study in humans which reported that the greatest inhibition by contralateral acoustic stimulation of evoked otoacoustic emissions (EOAEs) was obtained on the lower EOAE frequency components (Morand et al., 2000). In contrast, for half-octave-band noise, in the data from both this chapter (e.g. Fig. 6A) and from Chapter 3, there was a strong pattern of MOC effect increasing as probe frequency decreased.

That the MOC effect strength appears to decrease with increasing probe frequency is not expected from MOC anatomy and physiology in animals (Guinan et al., 1984) and MOC anatomy in humans (Schrott-Fischer et al., 1994); MOC innervation is largest in the upper basal turn of the cochlea and declines going toward the apex. In animals, it is thought that cochlear amplification decreases and basilar membrane (BM) responses become more linear as one proceeds apically (Robles and Ruggero, 2001). Since MOC activation reduces cochlear amplification and decompresses the BM response growth, there appears to be little opportunity for action by MOC efferents at low frequencies in animals. Although species differences cannot be ruled out, there is no reason to expect them. At present, it is unknown by what mechanisms MOC efferents produce larger effects at low frequencies but a likely candidate is the pattern of activation produced by the central part of the MOC acoustic reflex.

V. Conclusion

In conclusion, MOC effects increased as elicitor bandwidths increased regardless of whether the noise bands were centered at the probe or at an apical frequency region remote from the probe. Since the elicitor sound level was kept constant, the increase in MOC effects can be attributed directly to the increase in elicitor bandwidth, i.e. the effect of increased spatial summation from wider noise bands was more than the effect of decreasing the elicitor spectral level near the probe frequency. The largest elicitor-induced ΔSFOAE magnitudes were for 0.5 kHz probes and the smallest for 4 kHz probes for half-octave noise bands but for wide-band noise, 0.5 and 1 kHz probes showed responses of similar amplitude. These suggest that the strength of the MOC acoustic reflex is controlled more by central factors than peripheral innervation. Activation of the MOC reflex inhibited the SFOAE magnitude and/or induced a phase lead in the SFOAE, although these two changes need not occur together. In general, phase leads in the inhibited SFOAE were found to increase with elicitor bandwidth. Lastly, MOC effects, in terms of ΔSFOAE magnitudes, from increasing elicitor bandwidths calculated from measurements of the ΔSFOAEs from half-octave noise bands well-approximated the measured changes in MOC effects with elicitor bandwidth, but showed a consistent over estimation for ipsilateral and bilateral elicitors. Our results reveal that efferents from over almost the entire cochlear length can collectively affect the mechanical response at a specific cochlear place.

VI. Appendix

Measuring the low-frequency edge of two-tone suppression

To study MOC effect as a function of elicitor bandwidth for elicitors centered at a frequency below the probe frequency, we carried out initial studies to determine how far the elicitor frequency should be below the probe so that the widest elicitor produced no significant two-tone suppression of the SFOAE from the probe. If the elicitor produces no two-tone suppression, then MOC effects can be averaged in the during-elicitor window (2550-2950ms) near the end of the elicitor presentation when the MOC effect is greatest. This would yield a higher measured MOC effect and would reduce the number of experimental repeats needed to achieve statistically significance in the results. To choose an elicitor frequency range that falls outside the frequency band for two-tone suppression of the probe SFOAE, we first had to know the frequency range of two-tone suppression of the SFOAE.

Estimation of Two-Tone-Suppression Frequency Band

During the initial phase of this study, the frequency range for significant two-tone suppression was obtained for a few subjects. To do this we used data from the experiments of Chapter 3 in which 60 dB SPL tone elicitors were swept in half-octave frequency steps around 1 and 4 kHz, 40 dB SPL probe tones. The timing of the stimuli was as in Fig. 1A. The suppression was measured in a 30 ms time window delayed 20 ms delay from the suppressor onset (at 520-550 ms in Fig. 1A). This window was chosen to be optimum for estimating the amount of two-tone suppression without significant MOC effects. Since the MOC acoustic reflex in humans has an onset time constant on the order of 200+ ms (Backus and Guinan, 2006), there should be little MOC effect in this time window. On the other hand, two-tone suppression operates on a much shorter time scale of a few ms in the cochlea, and because of OAE travel time, on a scale of 10s of ms in the SFOAE (Guinan, 1990). Since typical SFOAE latencies in humans are approximately 15 cycles (Zweig and Shera, 1995), which translates to latencies of approximately 15 ms and 3.7 ms for the 1 kHz and 4 kHz probe respectively, the 20ms delay from the elicitor onset should have provided sufficient time for the full effect of two-tone-suppression on the SFOAE to be measured in the ear canal.

Figure 10 shows two-tone suppression measurements from three subjects at 1 and 4 kHz. The cut-off frequency at which suppression was considered to be insignificant was taken to be the frequency at which the suppression magnitude fell to less than 2.5 standard deviations above the noise mean. On the average, for a 60 dB SPL suppressor tone, the lower-limit suppression frequency was approximately 1.3 octaves below the 1 kHz probe and approximately 1 octave below the 4 kHz probe. The upper limit was more variable, but unimportant for present purposes because off-probe-frequency elicitor bandwidth series were only done with bandwidths centered below the probe frequency. From these data, the off-probe-frequency elicitor center frequencies were chosen to be at 2 octaves below the probe frequency and the widest off-centered elicitor bandwidth was chosen to be at 2 octaves. With the widest off-centered elicitor noise band of 2 octaves, the upper frequency edge of the elicitor was at 1 octave below the probe. Elicitor noise bands were kept at a constant energy level of 60 dB SPL so the spectral level was significantly lower than the 60-dBSPL tone suppressor used to estimate the two-tone suppression frequency band in Fig 10. For all subjects, magnitude of the ΔSFOAE averaged within the two-tone-suppression-window (520-530ms) in the presence of the 2 octave off-centered noise-band was not significantly different from the noise floor at the 0.05 level (Student's t-test). Hence, the during-elicitor measure from these noise bands was due to activation of the MOC reflex and not two-tone suppression.

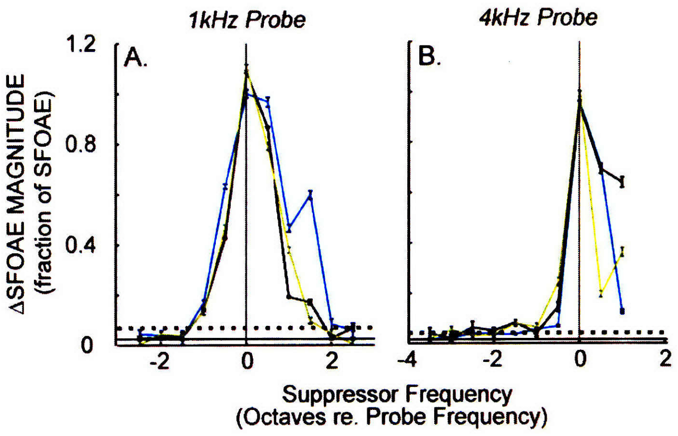

Figure 10: Two-tone suppression from a 60 dB SPL tone, as shown by the change in the SFOAE, ΔSFOAE, versus suppressor frequency re the probe frequency from 3 subjects. Error bars represent 1 standard error of the mean. The blue, green and black curves (-•-) represent measurements from different subjects. The horizontal solid and dashed lines represent the average noise floor and 2.5 standard deviations above the average noise floor, respectively.

VII. Reference

Bacon, S.P. and Smith, M.A. (1991). 'Spectral, intensive and temporal factors influencing overshoot,' Q. J. Exp. Psychol. A. 43(3):373-399.

Backus, B.C. (2005). 'Using Stimulus Frequency Otoacoustic Emissions to study basic properties of the human medial olivocochlear reflex,' Ph.D. Thesis, MIT, Chapter 2: 12-18.

Backus, B.C. (2007). 'Bias due to noise in otoacoustic emission measurements,' J Acoust Soc Am 121(3):1588-1603.

Backus, B.C. and Guinan, J. J. Jr.. (2006). 'Time-course of the human medial olivocochlear reflex,' J. Acoust. Soc. Am. 119(5 Pt 1): 2889-904.

Brown, M.C., Kujawa, S.G., Duca, M.L. (1998). 'Single olivocochlear neurons in the guinea pig. I.: Bilateral facilitation of responses to high level noises,' J. Neurophys. 79(6): 3077-3087.

Cooper, N.P. and Guinan, J.J. Jr. (2003). 'Separate mechanical processes underlie fast and slow effects of medial olivocochlear efferent activity,' J. Physiol. 548(Pt 1): 307-312.

Guinan, J.J. Jr., Warr, W.B., and Norris, B.E. (1984). 'Tonotopic organization of the olivocochlear projections from lateral and medial zones of the superior olivary complex,' J. Comp. Neurol. 226: 21-27.

Guinan, J. J., Jr. (1990). "Changes in stimulus frequency otoacoustic emissions produced by two-tone suppression and efferent stimulation in cats," in *Mechanics and Biophysics of Hearing*, edited by P. Dallos, C. D. Geisler, J. W. Matthews, and C. R. Steele (Springer Verlag, Madison, Wisconsin), pp. 170-177.

Guinan J.J. Jr. (1996). 'The physiology of olivocochlear efferents,' In: Dallos P.J., Popper A.N., Fay, R.R. (eds.), The Cochlea. New York: Springer-Verlag, pp.435-502.

Guinan, J.J. Jr., Backus, B., Lilaonitkul, W, Aharonson, V. (2003). 'Medial olivocochlear efferent reflex in humans: otoacoustic emission (OAE) measurement issues and the advantage of stimulus frequency OAEs, J Assoc Res Otolaryngol 4(4):521-540.

Kawase, T., Delgutte, B., Liberman, M.C. (1993). 'Anti-masking effects of the olivocochlear reflex, II: Enhancement of auditory-nerve response to masked tones,' J. Neurophysiol. 70: 2533-2549.

Maison, S., Micheyl, C., Andeol, G., Gallego, S., Collet, L. (2000). 'Activation of olivocochlear efferent system in humans: influence of stimulus bandwidth,' Hear Res 140:111-125.

McFadden, D., (1989). 'Spectral Differenced in the ability of temporal gaps to reset the mechanisms underlying overshoot,' J. Acoust. Soc. Am. 85(1):254-261.

Morand, N., Khalfa, S., Ravazzani, P., Tognola, G., Grandori, F., Durrant, J.D., Collet, L., Veuillet, E. (2000). 'Frequency and temporal analysis of contralateral acoustic stimulation on evoked otoacoustic emissions in humans,' Hear. Res. 145(1-2): 52-58.

Robles, L. and Ruggero, M.A. (2001). 'Mechanics of the mammalian cochlea,' Physiol. Rev. 81(3): 1305-1352.

Schrott-Fischer, A., Egg, G., Kong, W.J., Renard, N., Eybalin, M. (1994). 'Immunocytochemical detection of choline acetyltransferase in the human organ or Corti,' Hear. Res. 78(2): 149-157.

Schmidt, S. and Zwicker, E. (1991). 'The effect of masker spectral asymmetry on overshoot in simultaneous masking,' J. Acoust. Soc. Am. 89:1324-1330.

Strickland, E. A. (2001). 'The relationship between frequency selectivity and overshoot,' J. Acoust. Soc. Am. 109, 2062-2073.

Turn, C.W. and Doherty, K.A. (1997). 'Temporal masking and the 'active' process in normal and hearing impaired listeners,' in Modeling Sensorineural Hearing Loss, edited by W. Jesteadt (Earlbaum, Hillsdale, NJ), pp. 386-396.

Von Klitzing, R., and Hohlrausch, A. (1994). 'Effect of masker level on overshoot in running- and frozen-noise maskers,' J. Acoust. Soc. Am. 95:2192-2201.

Zeng, F.G., Martino, K.M., Linthicum, F.H., and Soli, S.D. (2000). 'Auditory perception in vestibular neurectomy subjects,' Hear. Res. 142: 102-112.

Zweig, G. and Shera, C. A. (1995). 'The origin of periodicity in the spectrum of evoked otoacoustic emissions,' J. Acoust. Soc. Am. 98(4): 2018-2047.

Zwicker, E. (1965). 'Temporal effects in simultaneous masking and loudness,' J. Acoust. Soc. Am.38: 132-141.

Chapter 5: Effects of Ipsilateral versus Contralateral Elicitors on Stimulus Frequency Otoacoustic Emissions as Functions of Elicitor Frequency Content

Abstract

To investigate the relative effects of ipsilateral and contralateral medial olivocochlear (MOC) reflexes in humans, changes in otoacoustic emissions elicited by a variety of acoustic stimuli were measured. The metric used was the elicitor-induced change in the stimulus frequency otoacoustic emission (ΔSFOAE) from a 40-dB SPL tone near 0.5, 1 or 4 kHz. Elicitors were kept constant at 60 dB SPL and were presented to either the ipsilateral or contralateral ear. Four experiments were done. In the first two experiments, narrow frequency regions above and below the probe frequency were systematically targeted with either a tone or a half-octave-band noise elicitor. In the third experiment, the effect of elicitor bandwidth was explored with noise bands centered at the probe frequency. In the last experiment, the elicitor bandwidth was varied for noise bands centered two octaves below the probe frequency such that the spectral contents did not include the probe frequency. The results show that for 0.5, 1 and 4 kHz probe frequencies, the ΔSFOAE magnitude from ipsilateral elicitors was significantly greater than the ΔSFOAE magnitude from contralateral elicitors only when the elicitor had frequency components close to the probe frequency. The difference between the ipsilateral and contralateral ΔSFOAE magnitudes diminished for elicitor tones with frequencies remote from the probe frequency, noise bands centered two octaves below the probe frequency, and broadband noise (0.1-10 kHz). For elicitors both at and remote from the probe frequency, the relative effects from ipsilateral versus contralateral elicitors did not appear to be a function of probe frequency. If, as past work indicates, ΔSFOAEs are only produced by MOC effects, the data indicate that the relative ipsilateral/contralateral reflex strength in humans is influenced more by central processing than by the relative anatomical fiber count of the ipsilateral and contralateral MOC efferent fibers along the cochlea. However, an alternate explanation is that the increased ΔSFOAE magnitude for ipsilateral elicitors close to the probe frequency is due to cochlear intrinsic factors affected by the elicitor. A viable hypothesis is that all of the observed ΔSFOAEs are due to the combined action of MOC fibers and type II auditory-nerve fibers which form an interacting neural network under, and forming synapses with, outer hair cells.

Abbreviations

BBN	Broadband Noise	**OAE**	Otoacoustic Emission
BM	Basilar Membrane	**OCBW**	Off-Centered Bandwidth (centered 2 octaves below probe frequency)
BW	Bandwidth		
MEM	Middle-Ear Muscle	**SFOAE**	Stimulus Frequency Otoacoustic Emission
MOC	Medial Olivocochlear	**SEM**	Standard Error of the Mean
NBN	Half- Octave Noise band	**ΔSFOAE**	Complex change in the SFOAE (MOC Effect)

I. Introduction

The medial olivocochlear (MOC) efferents form a descending pathway from higher processing centers that relay gain control instructions to outer hair cells in the cochlea, resulting in a direct alteration of the mechanical basilar membrane (BM) response and an indirect change on auditory nerve fiber firing responses (for a review, see Guinan, 1996). There are many theories on the putative role of medial efferents in hearing. Examples include the enhancement of dynamic range and the improvement of signal-to-noise in the periphery (e.g. Kawase et al., 1993). The efferent system is organized binaurally but all the proposed functional roles of the acoustic MOC reflex only require a monaural system. Hence, there must be some further significance for the system's binaural organization and so the exploration of the MOC reflex laterality is essential for furthering our understanding of the efferent system.

Efferent fibers can be separated into fibers that are primarily activated by ipsilateral sounds and fibers that are primarily activated by contralateral sounds. In cats, it has been shown that the *average* ratio between the populations of these two types of fibers is approximately 2 to 1 (Liberman and Brown, 1996). This physiological finding provided a close match to cat anatomical data which showed that the *average* ratio between the innervation density of these two types of monaurally-activated efferent fibers was also approximately 2 to 1 (crossed medial efferents / uncrossed medial efferents)[19] (Guinan et al., 1984). However, in humans, MOC effects produced by ipsilateral elicitors were approximately equal to MOC effects produced by contralateral elicitors, for broadband elicitors and 1 kHz probes (Backus and Guinan, 2007). Aside from possible inter-species differences, this difference in human and cat relative ipsilateral/contralateral physiology might reflect a frequency-dependence in the relative ipsilateral / contralateral organization as found by Guinan et al. (1984).

The purpose of this study is to quantify the difference between the ipsilateral and contralateral MOC effects in humans as efferents are activated from different cochlear regions. MOC effects are quantified as the magnitude of the elicitor-induced change in the stimulus frequency otoacoustic emissions evoked by probe tones of different frequencies. Specifically, the study will focus on the ipsilateral and contralateral MOC effects at cochlear regions of 0.5, 1 and 4 kHz. To see MOC effects elicited from different cochlear frequency regions relative to the probe frequency, narrow cochlear regions will be stimulated systematically in a swept-tone and a swept-half-octave-noise band experiment. To further explore the effects of simultaneously recruiting efferents over wider cochlear regions, elicitors of various bandwidths will be used under two different paradigms: (1) with the noisebands centered at the probe and (2) with the noisebands centered at two octaves below the probe. The results reveal that MOC effects produced by ipsilateral elicitors were significantly greater than MOC effects produced by contralateral elicitors for elicitor frequencies near the probe frequency. However, ipsilateral and contralateral elicitors at frequencies remote from the probe frequency gave rise to MOC effects that were approximately equal.

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[19] Guinan et al. categorized the efferents as 'crossed' and 'uncrossed', which are anatomical terms. Later findings revealed that the crossed medial efferents are activated by ipsilateral acoustic stimuli while the uncrossed medial efferents are activated by contralateral acoustical stimuli.

II. Methods and Analysis

A. Subjects

All subjects included in this study had clinically normal hearing thresholds in both ears (within 20 dB re. ANSI pure tone threshold from 250 Hz to 4 kHz). Measurements were conducted in a sound-proof room. A warning light was automatically turned on before each stimulus presentation and the subject was instructed to sit still during the time that the light was on and sounds were presented. Subjects were rejected from the study if 1) the subject's middle-ear muscle (MEM) contractions were significant at the stimulus levels used for the experiments (See MEM-test in section D), 2) the subject was unable to remain awake and sit still during the experiment, or 3) the subject did not return to complete the study. A minimum SNR criterion of 3 (~9.5 dB) was applied to each data set to minimize amplitude estimation bias resulting from low SNR (Backus, 2007). This minimum SNR criterion was set to avoid significant amplitude estimation biases resulting from low SNR (Backus, 2007). The 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. The number of ears and subjects involved in this study are summarized in table 1.

Probe Frequency Region	Experiment Type	Subjects Included		Number of Ears	Age Range (Years)	Average Age (Years)
		Male	Female			
0.5 kHz	Swept-tone	1	4	8	22-31	24.4
	Swept-NBN	1	4	8	22-31	24.4
	BW	1	2	5	22-35	27
	OCBW	-	-	-	-	-
1.0 kHz	Swept-tone	3	4	11	22-33	27.5
	Swept-NBN	3	4	11	22-23	27.5
	BW	4	4	10	21-28	24.6
	OCBW	2	3	6	21-25	23.2
4.0 kHz	Swept-Tone	0	3	3	22-40	28
	Swept-NBN	1	6	7	22-40	28
	BW	1	4	6	21-32	23.6
	OCBW	0	3	3	22-35	27

Table 1: Summary of subject gender, subject age and the number of subjects included in the study. *Swept-Tone* and *Swept-NBN* refer to experiments in which the elicitor frequencies of tones, or half-octave noise bands, were varied relative to the probe frequency. *BW* refers to experiments in which the elicitor bandwidth was varied, for noise bands centered at the probe frequency. *OCBW* refers to experiments in which the elicitor bandwidth was varied, for noise bands centered two octaves below the probe frequency.

B. Acoustic Stimuli

As a probe sound to evoke SFOAEs in both ears, a 40-dB SPL continuous tone[20] selected at a frequency within ±10% of 0.5, 1 or 4 kHz was presented bilaterally through the earphones of 2 Etymotic ER10C acoustic assemblies. For each subject, a probe frequency was selected that: (1) was at least 100 Hz away from any spontaneous OAE with magnitude above -10 dB SPL (this was done to avoid possible entrainment – van Dijk, et al., 1988), and (2) produced the largest ΔSFOAE magnitude to a 60 dB SPL, contralateral broad-band noise (so that the signal/noise ratio (SNR) criteria could be reached with the smallest number of stimulus repeats).

To elicit MOC activity, a 60 dB SPL noise band was presented ipsilaterally, contralaterally or bilaterally for 2.5 s. Preceding the elicitor was a 0.5 s onset period from which the baseline response was measured, and following the elicitor was a 2 s period for recovery. The resulting stimulus repetition period was 5 s (Fig. 1A). Three types of experiments were done. Details of these experiments can be found in sections B1, B2 and B3. In each experiment elicitors were presented in a randomized order to avoid bias.

The baseline SFOAE (the SFOAE preceding the MOC elicitor) was measured from the vectorial difference of the ear-canal sound pressure from the 40 dB SPL probe tone with and without a 60 dB SPL suppressor tone at 110 Hz below the probe frequency[21]. The baseline SFOAE vector was measured separately from the induced-change in SFOAE in runs in which the suppressor was presented for 0.5 s every 1 s (Fig. 1B). For both suppressor-tones and MOC-elicitors, 5-ms rise/fall cosine ramps were introduced at the presentation edges to minimize spectral splatter. Consecutive elicitor or suppressor presentations had opposite polarities so that upon averaging their acoustic waveforms would cancel leaving a residual measure equal to the amount of induced change in the SFOAE vector.

Calibrations of the acoustic output from the two sound sources in each ER10C acoustic assembly were done (using the microphone in the ER10C) at the beginning of every data gathering session and frequently within a session. Noise bursts were made to be spectrally flat by applying these calibrations.

B1. Experiment 1: Swept-Tone or Swept-NBN Frequency Series

In the first experiment, MOC effects due to ipsilateral versus contralateral elicitors were compared as functions of elicitor frequency relative to the probe frequency. To do this, narrow cochlear regions were targeted for MOC activation with either tone or NBN elicitors (60 dB SPL) that were presented in half-octave steps at elicitor frequencies from 2 octaves below to 2 octaves above the 0.5 kHz probe, from 2.5 octaves below to 2.5 octaves above the 1 kHz probe, or from -3.5 octaves below and 1 octave above the 4 kHz probe.

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[20] Contralateral tones at the probe frequency presented at 40 dB SPL were found to be weak elicitors of efferent response (Guinan et al., 2003).

[21] Backus and Guinan (2007) found that the SFOAE obtained using these parameter values can underestimate the true SFOAE amplitude, i.e. the suppressor produces only 80-100% suppression. The variability in the *degree* of underestimation could have increased the standard error of our group averages. However, underestimation of the SFOAE magnitude did not affect the shape of the MOC effect curves because, for a given ear, all points were normalized by the same SFOAE measure.

B2. Experiment 2: Bandwidth effects (BW)

In the second experiment, MOC effects due to ipsilateral versus contralateral elicitors were compared as functions of elicitor bandwidth for noise bands centered at the elicitor frequency. 60 dB SPL noise-band elicitors were centered (on a logarithmic scale) at the probe frequency. For 0.5 and 1 kHz probes, the noise bandwidths were 0.5, 1 ,2 and 4 octaves, and for the 4 kHz probe the noise bandwidths were 0.5, 1, 2 octaves. In addition, for all probe frequencies, broadband noise (BBN) (0.1 - 10 kHz) was presented and became the widest elicitor band. Since the BBN stimulus was not centered on the probe frequencies of 0.5 and 4 kHz, in the figures BBN points are shown connected to the other points with dashed lines. The bandwidth series and the BBN stimulus were different data sets so the SNR criterion that the maximum point must have a SNR > 3 (~9.5 dB) was applied to each separately.

B3. Experiment 3: Off-probe-centered bandwidth effects (OCBW)

In the third experiment, MOC effects due to ipsilateral versus contralateral elicitors were compared as functions of elicitor bandwidth for noise bands centered (on a logarithmic scale) two octaves below the probe frequency. This was done to determine if any changes observed in the ipsilateral versus contralateral relative MOC effects with increasing noise bandwidth depended on the noise band being centered on the probe tone. In this experiment, noise bands with bandwidths of 0.5, 1, 1.5 and 2 octaves were used, and data were obtained only for 1 and 4 kHz probes. One advantage of these off-centered noise bands is that they did not have frequency components near the probe frequency and did not produce significant two-tone suppression (see Appendix of Chapter 4). Thus we were able to measure the MOC effects in a window during the elicitor (see below).

C. Measurement Analysis

Responses were rejected as being contaminated with artifacts when the difference between one pair of responses and the next pair exceeded a criterion. Stimulus pairs were used because elicitors (or suppressors) were alternated in polarity across stimulus repetitions. Multiple response pairs were vectorially averaged to achieve response averages with $N \geq 12$ stimulus repetitions. The averaged waveforms were then heterodyned to obtain the complex waveform of the response at the probe frequency. Details of the heterodyning method and specification of the frequency domain filtering can be found elsewhere (Guinan et al, 2003).

The complex amplitude of the ear canal sound pressure at the probe frequency, P(t), is the sum of the probe-tone and the evoked SFOAE(t) complex amplitude. An MOC elicitor, or a suppressor, can induce a change in the SFOAE and thereby change P(t). Changes in the SFOAE(t), ΔSFOAE(t), were calculated from P(t) by the vectorial difference between P(t) and $P_{baseline}$ where $P_{baseline}$ is the vector average of P(t) between 50-450 ms, i.e. the average P(t) before the onset of the suppressor or MOC elicitor (see Guinan 2003 for more detail). The MOC-induced change was then expressed as a fraction of the SFOAE by dividing ΔSFOAE(t) by the baseline SFOAE vector. That is,

$$\Delta\text{SFOAEn}(t) = \frac{P(t) - P_{\text{Baseline}}}{\text{SFOAE}} = \frac{\Delta\text{SFOAE}}{\text{SFOAE}} \qquad \text{(eq. 1)}$$

where,

$P(t)$ = the complex heterodyned measurement, and $0 < t < 5$s.

P_{Baseline} = the vectorial average of $P(t)$, and $0.05 < t < 0.45$s

SFOAE = the complex baseline stimulus frequency otoacoustic emission evoked by the probe tone.

ΔSFOAEn(t) = the change in the SFOAE normalized by the baseline SFOAE.

In the above, SFOAE(t) and ΔSFOAE(t) were the raw, un-normalized values and ΔSFOAEn(t) was the normalized value. In all of the remaining, we will use only the normalized values and will drop the "n" so that henceforth ΔSFOAE(t) = ΔSFOAEn(t) of above. A vector diagram of the ear canal sound pressures can be found in Figure 2.

Normalized ΔSFOAE(t) data were vectorially averaged in either a 0.4 s "during-elicitor" time window ending 0.05 s before the end of the elicitor (for contralateral ΔSFOAE(t)), or a 0.1 s "post-elicitor" time window starting at 0.05 s after the end of the elicitor (for ipsilateral and bilateral Δ SFOAE(t) and, for comparison, contralateral ΔSFOAE(t)). Averaging in the post-elicitor window avoids two-tone-suppression effects of the probe that can be evoked by ipsilateral and bilateral elicitors, but at the expense of capturing the MOC effect during its decay. Two-tone-suppression is absent for contralateral elicitors so the contralateral ΔSFOAE(t) can be averaged from a during-elicitor window near the end of the elicitor presentation which allows us to capture the maximum MOC effect elicited. The noise floor estimate was obtained from averaging the ΔSFOAE(t) in a time-window of the same duration as the (during or post-elicitor) data-analysis time window, but positioned such that the end of the noise time window was 50 ms before the end of a stimulus repetition period.

The relative amplitudes of the MOC effects produced by ipsilateral and contralateral elicitors was quantified by the "*Fractional Difference*" defined as the difference between the ipsilateral and contralateral ΔSFOAE magnitudes as a fraction of the ipsilateral ΔSFOAE magnitude. That is:

$$\mathit{Fractional\ Difference} = \frac{|\Delta SFOAE_{Ipsi}| - |\Delta SFOAE_{Contra}|}{|\Delta SFOAE_{Ipsi}|} \qquad \text{(eq. 2)}$$

The *Fractional Difference* shown in the plots was obtained by first calculating the *Fractional Difference* separately for each subject and averaging the values across subjects.

D. Middle-ear-muscle (MEM) contraction test

A MEM test was performed on each subject to ensure that the MEMs were not activated at the stimulus levels used. In this test, a 65 dB SPL continuous suppressor tone at 110 Hz above the probe frequency was presented in addition to the normal acoustic stimuli. With this paradigm, only MEM contractions produce a change in the sound pressure at the SFOAE probe frequency. Thus, 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 has been no significant MEM contraction. Details of the experimental rational can be found in the Methods section of Chapter 2.

E. Determining the statistical significance of variations across parameters

To determine the statistical significance of the variations of MOC effect 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 MOC effect results passed the Lillifores test for normality. If they did not pass, the Friedman non-parametric two-way ANOVA was used. Statistical significance was accepted at the 0.05 level. The data were compared to a control data set that measured the response under the Null-hypothesis of no MOC effect. The control data were the noise floor measurements taken from a time-window of the same duration as the (during or post-elicitor) data-analysis time window, but positioned such that the end of the noise time window was 50 ms before the end of a stimulus repetition period.

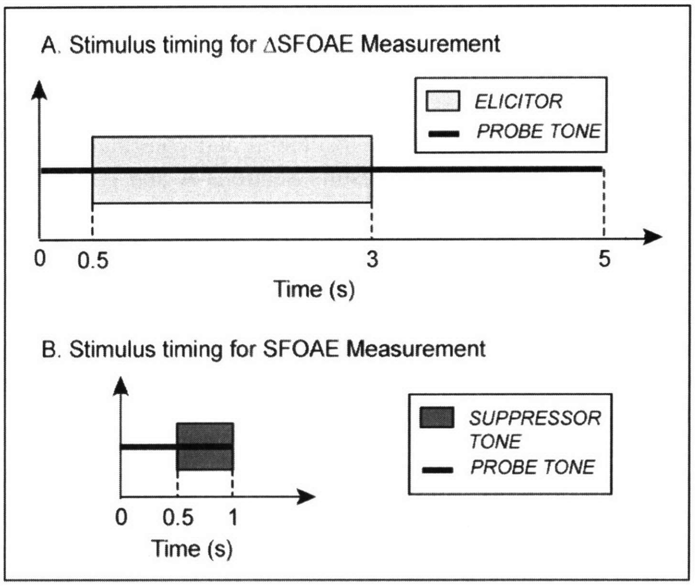

Figure 1. Temporal presentation of stimuli. A. For the measurement of the elicitor-induced ΔSFOAE, there was an initial delay of 0.5 s to establish the baseline response, then a 2.5 s tone or noise burst to elicit MOC activity, followed by a 2 s recovery period. This stimulus pattern was repeated every 5 s with the polarity of the elicitor alternated so that upon averaging the measurements, the elicitors would cancel leaving a residual pressure equal to elicitor-induced ΔSFOAE. **B**. For the SFOAE measurement, there was an initial delay of 0.5 s to establish the baseline response, then a 0.5 s suppressor tone at 110 Hz below the probe frequency. This stimulus pattern was repeated every 1 s with the polarity of the suppressor alternated.

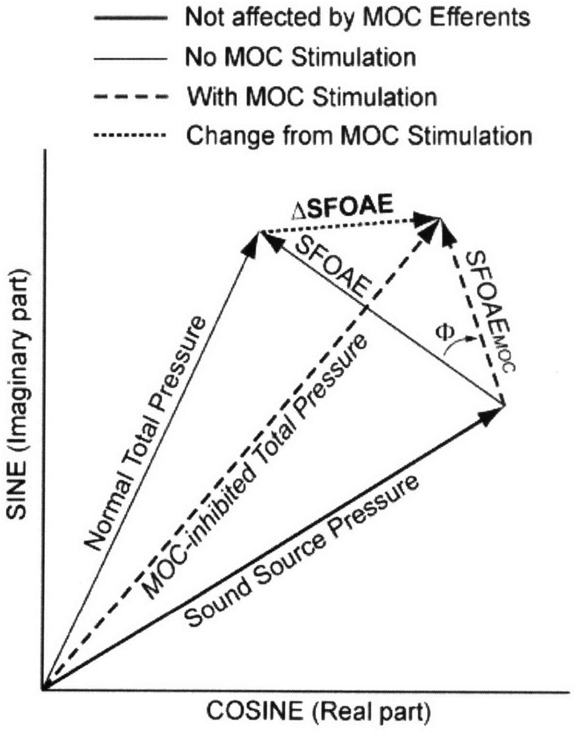

Figure 2. Vector diagram of MOC-elicitor effects on sound pressures in the ear canal. The arrows are vectors in the complex plane such that the length of the arrow represents the magnitude and the direction of the arrow represents the phase. Before stimulation by the MOC-elicitor, the *Sound Source Pressure* and the SFOAE summate to form the *Normal Total Pressure* in the ear canal. In the presence of an MOC-elicitor the SFOAE magnitude and phase are changed as shown by SFOAEMOC resulting in a new ear-canal sound pressure (*MOC-inhibited Total Pressure*). The change in the ear canal pressure shows the resulting change in the SFOAE, ΔSFOAE. Note that the angle ϕ shows the phase delay of SFOAEMOC from the SFOAE phase, opposite the sign convention used in the other figures.

III. Results

In this study, we measured ΔSFOAEs produced by ipsilateral and contralateral elicitors as functions of frequency for tone or half-octave-noise elicitors (Results Sections A and B), and as functions of elicitor bandwidth for noise-band elicitors centered at the probe frequencies, or 2 octaves below the probe frequencies (Results Sections C and D). The relative ΔSFOAE magnitudes due to ipsilateral versus contralateral elicitors were then quantified by the *Fractional Difference* between the ΔSFOAE magnitudes from ipsilateral and contralateral elicitors relative to the ΔSFOAE magnitude from the ipsilateral elicitor. For all of these experiments, MEM-tests revealed no significant MEM contractions in response to the stimulus levels used in this study. Hence, all of the measured elicitor-induced changes arose from within the cochlea, presumably due to MOC activity.

The *Fractional Difference* between the ipsilateral and contralateral ΔSFOAE magnitudes was found to vary with the proximity of the elicitor spectral contents to the probe-frequency region. In general, for elicitors that were close to the probe frequency, the ΔSFOAE magnitudes produced by ipsilateral elicitors were significantly greater than the ΔSFOAE magnitudes produced by contralateral elicitors. For elicitors that were far from the probe frequency, the ΔSFOAE magnitudes produced by ipsilateral and contralateral elicitors converged. The details of our results are as follows.

A. ΔSFOAE magnitudes from ipsilateral versus contralateral elicitors, as functions of tone-elicitor frequency.

The ΔSFOAE magnitudes produced by ipsilateral and contralateral tone elicitors are shown in Figure 3, top row, for probe frequencies near 0.5, 1 and 4 kHz. The *Fractional Differences* between the responses in the top row are shown in Figure 3, bottom row. Even though many of the points have large standard errors of the mean (SEMs), the variations in *Fractional Differences* with elicitor frequency were statistically significant (ANOVA: $P_{500Hz} = 0.006$; $P_{1kHz} = 0.018$; $P_{4kHz} = 0.009$). A major factor in producing this statistical difference is that the ipsilateral ΔSFOAE magnitude was larger than the contralateral ΔSFOAE magnitude consistently across individual subjects for elicitors at the probe frequency (note the very small SEMs of these points). The largest *Fractional Difference*, ~0.7, was for these points where the elicitor frequency equaled the probe frequency (Fig. 3, bottom). This implies that on the average, the contralateral ΔSFOAE magnitude was approximately 30% of the ipsilateral ΔSFOAE magnitude when elicited with a 60 dB SPL tone at the probe frequency. For off-probe-frequency elicitors, none of the *Fractional Differences* was significantly different from zero.

B. ΔSFOAE magnitudes from ipsilateral versus contralateral elicitors, as functions of half-octave-noise elicitor frequency.

The ΔSFOAE magnitudes produced by ipsilateral and contralateral half-octave noise-band elicitors, as well as the *Fractional Differences* derived from them, are shown in the top and bottom rows of Figure 4, respectively. The variations in the *Fractional Differences* with elicitor frequency were statistically significant at 1 and 4 kHz, but not at 0.5 kHz (ANOVA: $P_{500Hz} = 0.075$; $P_{1kHz} = 0.010$; $P_{4kHz} = 0.001$). In contrast to the tone data, the 1 and 4 kHz half-octave-noise elicitors produced significantly larger ipsilateral than contralateral ΔSFOAE magnitudes both for elicitors at the probe frequency and for elicitors ½ octave above the probe frequency. Moreover, for both probe frequencies, the values of the significant *Fractional Differences* (~0.5) were approximately the same for elicitors centered at the probe frequency and 0.5 octaves above the probe frequency. This implies that for 1 and 4 kHz half-octave noise-band elicitors centered at, and ½ octaves above, the probe frequency, the ΔSFOAE magnitudes from contralateral elicitors were approximately half the size of those from ipsilateral elicitors. For elicitor frequencies below the probe frequency, the ΔSFOAE magnitudes at 1 kHz were consistently greater for ipsilateral compared to contralateral elicitors, but none of these differences was statistically significant. For 4 kHz probes and elicitor frequencies below the probe frequency, the opposite was true, i.e. contralateral ΔSFOAE magnitudes were largest, but these were less consistent and, again, not significant.

C. ΔSFOAE magnitudes from ipsilateral versus contralateral elicitors, as functions of elicitor bandwidth.

The ΔSFOAE magnitudes produced by ipsilateral and contralateral elicitors as functions of elicitor bandwidths centered at the probe frequency, as well as the *Fractional Differences* derived from them, are shown in the top and bottom rows of Figure 5, respectively. The variations in the *Fractional Differences* with elicitor bandwidth were statistically significant at 1 and 4 kHz, but not at 0.5 kHz (ANOVA: $P_{500Hz} = 0.501$; $P_{1kHz} = 0.009$; $P_{4kHz} < 0.001$). The ΔSFOAE magnitudes (Fig. 5, top row) from both ipsilateral and contralateral elicitors increased with elicitor bandwidth and appeared to reach a plateau at the widest elicitor noise band, a broadband noise (0.1-10 kHz). For 1 and 4 kHz probes, the ΔSFOAE magnitude from ipsilateral elicitors was significantly greater than the ΔSFOAE magnitude from contralateral elicitors for narrow elicitor noise bands, but the difference in ΔSFOAE magnitudes decreased as elicitor bandwidth increased such that with the broadband-noise elicitor, the ipsilateral and contralateral ΔSFOAE magnitudes were not statistically different. The *Fractional Differences* (Fig. 5C and 5D) for the ½ and 1 octave noise bands were significantly different from 0 but the *Fractional Differences* for wider elicitor noise bands were not statistically different. The *Fractional Differences* for the ½ and 1 octave noisebands at 1 and 4 kHz probe frequencies were not significantly different and the average value came to about 0.5. That is, the ΔSFOAE magnitude from contralateral elicitors was approximately half the ΔSFOAE magnitude from ipsilateral elicitors, for elicitor noise bands with bandwidths ½ - 1 octave.

D. ΔSFOAE magnitudes from ipsilateral versus contralateral elicitors, as functions of elicitor bandwidth at 2 octaves below the probe frequency.

The ΔSFOAE magnitudes produced by ipsilateral and contralateral elicitors as functions of elicitor bandwidths centered two octaves below the probe frequency, as well as the *Fractional Differences* derived from them, are shown in the top and bottom rows of Figure 6, respectively. Almost all of the ipsilateral and contralateral ΔSFOAE magnitudes were statistically significant. These ΔSFOAE magnitudes increased with elicitor bandwidth, similar to the trend in Figure 5. However, unlike the results with the probe-centered noise bands of Figure 5, the *Fractional Differences* between the ipsilateral and contralateral ΔSFOAE magnitudes were not statistically different from zero, and the variations in the *Fractional Differences* with elicitor bandwidth were not statistically significant (ANOVA: $P_{1kHz} = 0.74$; $P_{4kHz} = 0.69$).

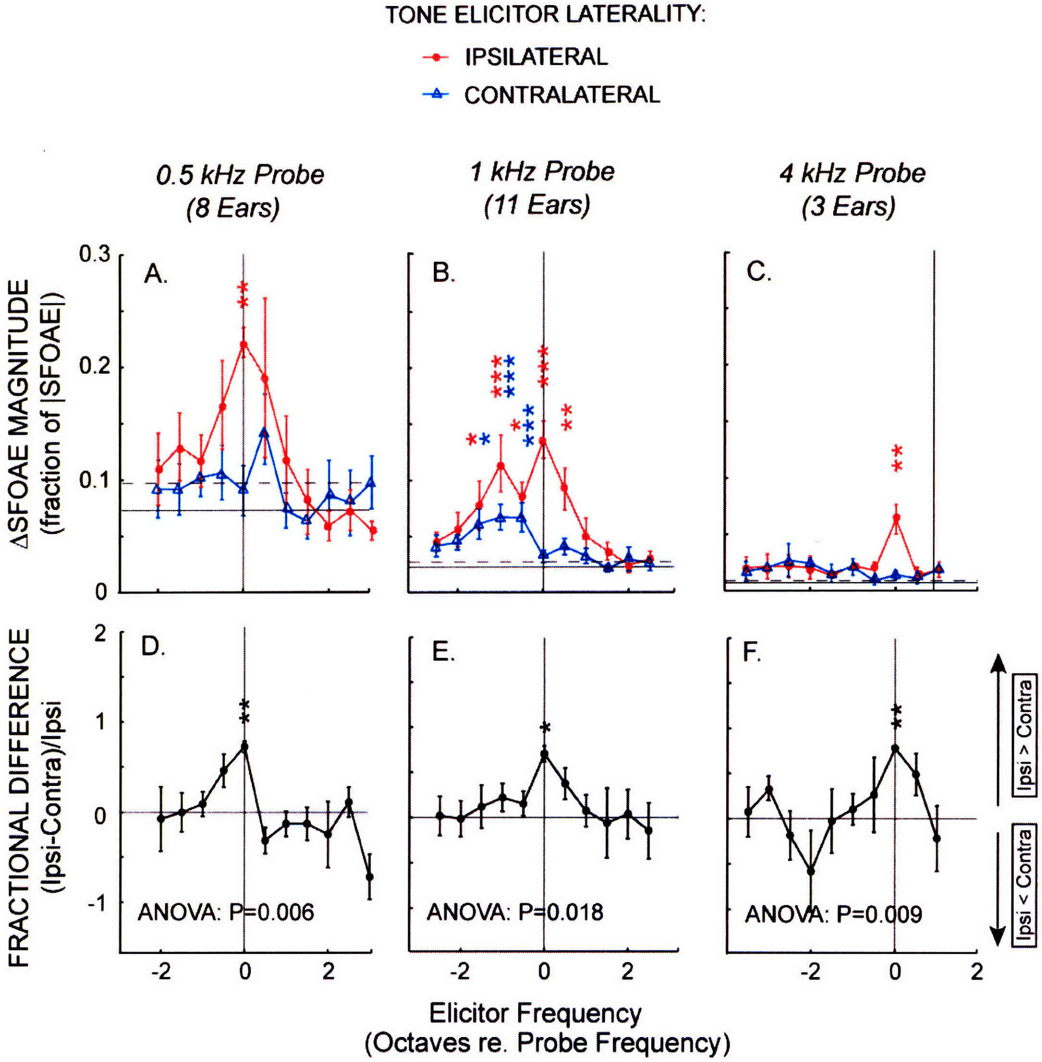

Figure 3: ΔSFOAE magnitude (top) and the ipsilateral-minus-contralateral *Fractional Difference* (bottom) as functions of elicitor frequency, for tone elicitors. Error bars are standard errors of the mean. Top: Elicitor-induced ΔSFOAE magnitudes from ipsilateral (red: —) and contralateral (blue: Δ) 60 dB SPL elicitors were measured in the post-elicitor window. Horizontal lines: Solid = noise-floor mean, dashed = 1 std. above the noise mean. Bottom: Fractional Differences. Significant differences from the noise floor (top) or from zero (bottom) are marked with asterisks: '*' ($P \leq 0.05$), '**' ($P \leq 0.01$), '***' ($P \leq 0.001$).

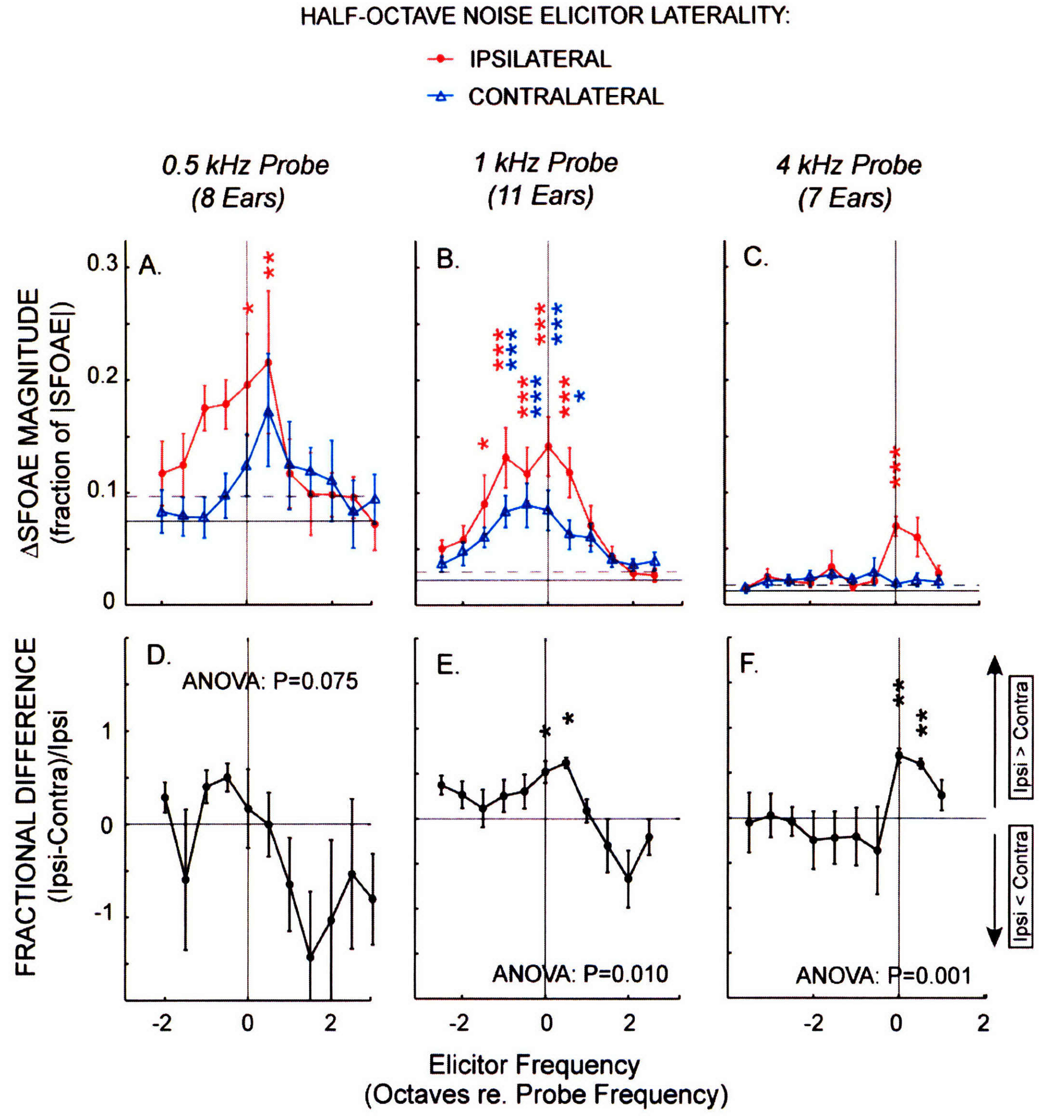

Figure 4: ΔSFOAE magnitude (top) and the ipsilateral-minus-contralateral *Fractional Difference* (bottom) as functions of elicitor frequency, for half-octave noise elicitors. Error bars are standard errors of the mean. Top: Elicitor-induced ΔSFOAE magnitudes from ipsilateral (red: —) and contralateral (blue: Δ) 60 dB SPL elicitors were measured in the post-elicitor window. Horizontal lines: Solid = noise-floor mean, dashed = 1 std. above the noise mean. Bottom: Fractional Differences. Significant differences from the noise floor (top) or from zero (bottom) are marked with asterisks: '*' ($P \leq 0.05$), '**' ($P \leq 0.01$), '***' ($P \leq 0.001$).

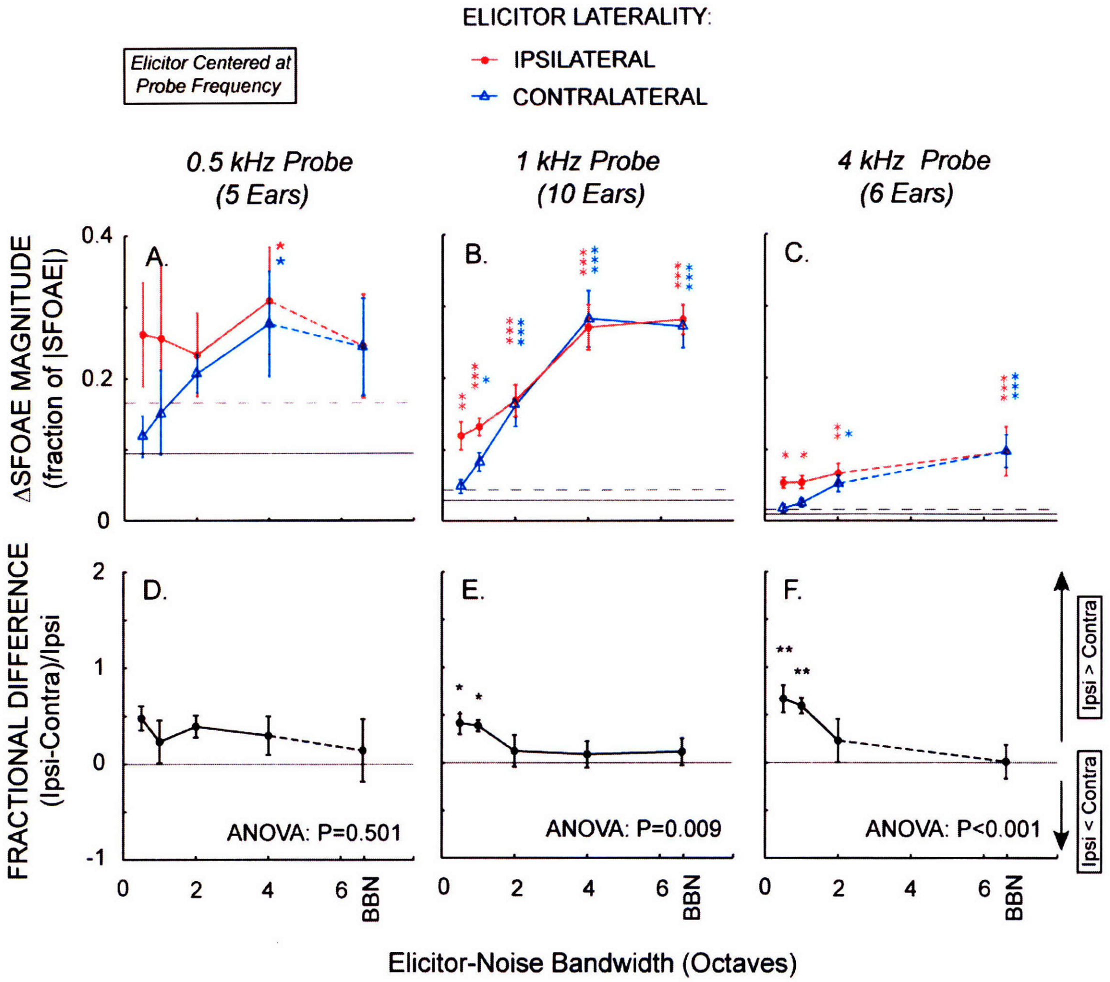

Figure 5: ΔSFOAE magnitude (top) and the ipsilateral-minus-contralateral *Fractional Difference* (bottom) as functions elicitor bandwidth. Elicitors were centered at the probe frequency. Error bars are standard errors of the mean. Top: Elicitor-induced ΔSFOAE magnitudes from ipsilateral (red: —) and contralateral (blue: Δ) 60 dB SPL elicitors were measured in the post-elicitor window. Horizontal lines: Solid = noise-floor mean, dashed = 1 std. above the noise mean. Bottom: Fractional Differences. Significant differences from the noise floor (top) or from zero (bottom) are marked with asterisks: '*' ($P \leq 0.05$), '**' ($P \leq 0.01$), '***' ($P \leq 0.001$).

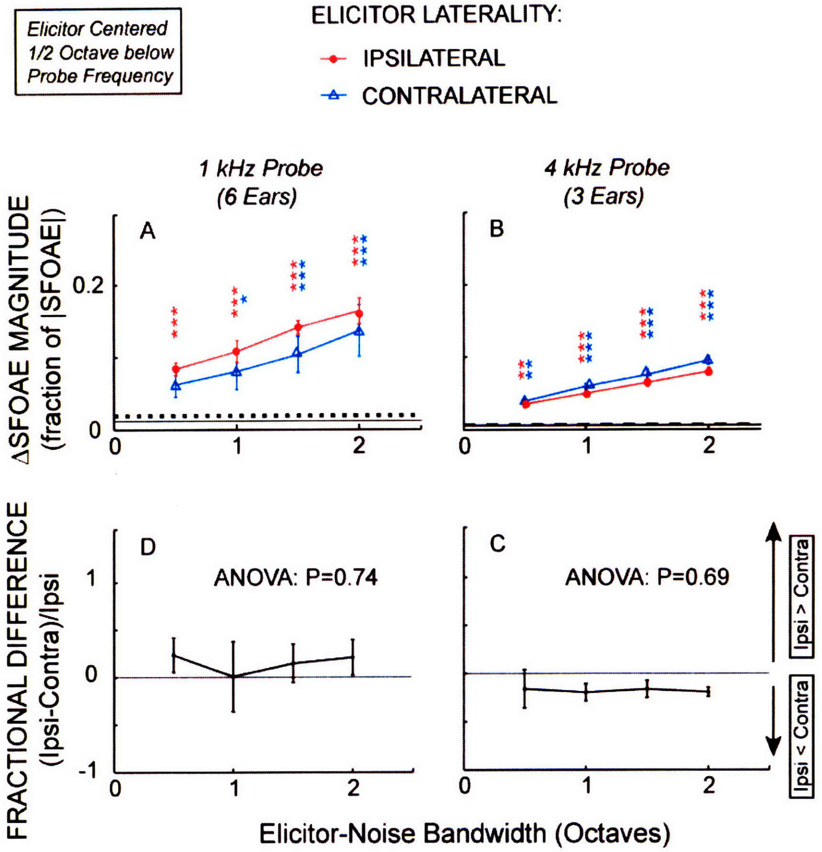

Figure 6: ΔSFOAE magnitude (top) and the ipsilateral-minus-contralateral *Fractional Difference* (bottom) as functions elicitor bandwidth. Elicitors were centered at 2 octaves below the probe frequency. Error bars are standard errors of the mean. Top: Elicitor-induced ΔSFOAE magnitudes from ipsilateral (red: —) and contralateral (blue: Δ) 60 dB SPL elicitors were measured in the post-elicitor window. Horizontal lines: Solid = noise-floor mean, dashed = 1 std. above the noise mean. Bottom: Fractional Differences. Significant differences from the noise floor (top) or from zero (bottom) are marked with asterisks: '*' ($P \leq 0.05$), '**' ($P \leq 0.01$), '***' ($P \leq 0.001$).

IV. Discussion

In general, the results show that ΔSFOAE magnitude was significantly greater when produced by ipsilateral, as compared to contralateral, elicitors for elicitors that were close in frequency to the probe frequency. When the elicitor frequency content was remote from the probe frequency, ipsilateral and contralateral elicitors produced ΔSFOAE magnitudes that were not statistically distinguishable, although there were sometimes differences that might be significant if enough data were obtained. These generalizations hold for the results from the swept-tone and swept-half-octave noise-band experiments, as well as the results from the on-frequency and off-frequency elicitor bandwidth experiments.

The results from the swept-tone, swept-half-octave-noise and centered-bandwidth experiments collectively point to a narrow cochlear frequency region where the difference between the ΔSFOAE magnitudes produced by ipsilateral and contralateral elicitors is maximal. This trend was most clearly observed for the 1 kHz and the 4 kHz regions. In the swept-frequency experiments, ΔSFOAE magnitudes from ipsilateral elicitors were significantly larger than ΔSFOAE magnitudes from contralateral elicitors for elicitors at the probe frequency, when using tone elicitors. However, when using noise-band elicitors, ΔSFOAE magnitudes were larger for ipsilateral than contralateral elicitors at, and one-half-octave above, the probe frequency. The exact boundaries of this "*Ipsi-Greater*" region are not clear, but judging from the patterns in Figures 2 and 3, the *Ipsi-Greater* region might extend from ¼ octave below to a half-octave or more above the probe frequency. The results from the centered-bandwidth experiments are consistent with this but do not help much in establishing the exact boundaries of the *Ipsi-Greater* region.

It seems noteworthy that the *Ipsi-Greater* region extends mostly to regions higher in frequency than the probe frequency, i.e. to elicitors that excite cochlear regions at, and basal, to the probe-frequency region. This coincides approximately with the frequency region where active negative damping by the cochlear amplifier has been calculated to take place – i.e. between the probe-tone CF region and 1 octave basal to CF (de Boer, 1996). This suggests that tones or noise-bands produce *Ipsi-Greater* responses when their spectral contents overlap in frequency with the cochlear regions that produce mechanical amplification.

The *Ipsi-Greater* response is produced by MOC efferents

The conceptual foundation on which the present work was based is that elicitor sounds excite MOC efferents through the MOC acoustic reflex. MOC fibers synapse directly on outer hair cells (OHCs), and MOC activity changes OHC properties thereby changing cochlear mechanical responses to sound (principally by turning down the gain of the cochlear amplifier). The MOC-induced changes in cochlear mechanical responses are monitored by the changes they produce in SFOAEs, ΔSFOAE. These ΔSFOAEs include both changes in the amplitude and changes in the phase of the SFOAE (see Chapter 3 Discussion for a more detailed discussion of how changes in the pattern of the traveling wave may affect SFOAE amplitude and phase). The interpretation that the ΔSFOAEs produced by sound elicitors are due to MOC effects is buttressed by the demonstration that similar ΔSFOAEs are produced by exciting MOC fibers with localized brainstem shocks (Guinan, 1990) and by experiments using sound-evoked MOC activity (which produces effects similar to those found with MOC shocks) in animals in which the MOC efferents were cut and the presumed MOC effect went away (e.g. Warren and Liberman, 1989a; Giraud et al., 1995; Kujawa and Liberman 2001). These lesion experiments provide perhaps the strongest evidence that the presumed sound-evoked MOC effects were indeed due to MOC efferents. Based on these experiments, we have interpreted our sound-elicited ΔSFOAEs as showing effects produced by MOC efferents. With this interpretation, our results show that larger MOC effects are produced by ipsilateral elicitors than by contralateral elicitors when the elicitor frequency is within the *Ipsi-Greater* region, and that similar MOC effects are produced by ipsilateral and contralateral elicitors with frequency contents outside of the *Ipsi-Greater* region. Since ipsilateral versus contralateral MOC innervation to a given probe frequency region is constant, this result implies that ratio of ipsilateral to contralateral MOC effects is greatly influenced by central processing. In favor of such an interpretation, there is ample evidence for complex central control over the firing patterns of MOC fibers (Liberman 1988).

The *Ipsi-Greater* response is produced by Cochlear Intrinsic Effects

Another possible interpretation of the increased ΔSFOAEs from ipsilateral elicitors in the *Ipsi-Greater* frequency region is that the increase is due to factors intrinsic to the cochlea, i.e. the increase is produced solely within the cochlea by the presence of the elicitor in the ipsilateral ear. Such intrinsic factors might include the accumulation of K^+ near OHCs, or a change in the OHC voltage operating point produced by the Type II neural network under OHCs. Of these two, the action of the neural network under OHCs formed by Type II auditory-nerve fibers seems more a more likely source of the *Ipsi-Greater* ΔSFOAEs that we measured. The Type II processes under OHCs form reciprocal synapses with OHCs and the efferent-like part of this reciprocal synapse has a post-synaptic cistern in the OHC (Francis & Nadol, 1993; Sato et al., 1997; Thiers et al., 2000; 2002). The significance of the OHC post-synaptic cistern is that MOC synapses on OHCs have a similar post-synaptic cistern. The cistern at the MOC synapse has been suggested to be the site of calcium-activated release of calcium that amplifies the response in the OHC (Sridhar et al., 1997). The calcium-activated calcium release is expected to take time to operate, perhaps producing the MOC onset time constant on the order of 100 ms, and more critically here, the time constant of the decay of MOC effects (also on the order of 100 ms). Since Type II efferent-like synapses on OHCs also have post-synaptic cisterns, they may also produce changes in OHCs on this same time scale, i.e. on the time scale of the decay of the ΔSFOAE that we measure in the post-elicitor window.

An example of a sound-induced intrinsic effect on an otoacoustic emission is provided by the onset adaptation of distortion-product otoacoustic emissions (DPOAEs) in cats. Liberman et al. (1996) found a rapid adaptation component (time constant ~100 ms, similar to typical MOC effects) which disappeared when MOC efferents were cut, and a slow adaptation component (time constant ~1 second) that did not disappear when all of the efferents were cut, i.e. this slow adaptation was due to cochlear intrinsic effects. Presumably the intrinsic changes within the cochlea were brought about by the presence of the primary tones that evoked the DPOAE and also elicited MOC activity in this experiment. This example shows that 60 dB SPL tones can cause intrinsic effects that affect DPOAEs. But we note, the 1 second onset time course of the intrinsic effects found by Liberman et al. (1996) is much longer than the ~100 ms time constant of the ΔSFOAE decays we see (Backus and Guinan, 2006). The two experiments are not comparable because DPOAEs and SFOAEs are produced by different cochlear processes (Shera and Guinan, 1999) and the Liberman et al (1996) experiment was done in anesthetized cats whereas our results are for awake humans.

Considering all of the above, a viable hypothesis is that the increased ΔSFOAEs from ipsilateral elicitors in the *Ipsi-Greater* frequency region are produced by cochlear intrinsic effects. Furthermore, the hypothesis that this cochlear intrinsic effect is due to Type II neural network on OHCs, although highly speculative, appears to be consistent with the data.

The *Ipsi-Greater* response is produced by a combined MOC and Type-II system

The type II neural network is intimately connected with MOC fibers and their intertwined anatomy suggests that they form part of a single system that influences OHCs. MOC fibers synapse on Type II fibers in the region under OHCs, on Type II fibers as they proceed to the OHC region, and, in humans, on the spiral ganglion cells of Type II neurons (Francis & Nadol, 1993; Sato et al., 1997; Thiers et al., 2000; 2002). One line of thought is that the MOC system acts, in part, through the type II neural system. Type II synapses on OHCs become denser going apically in the cochlea, in contrast to the MOC synapses which peak in the mid-basal region and become less dense going apically along the cochlea. Electrical stimulation of MOC fibers produces effects in the cochlea that decrease as one proceeds apically. However the pattern of MOC effect in the extreme apex is much stronger than would be expected based on the sparse MOC innervation in the apex (Guinan et al., 1984; Guinan and Gifford, 1988c; Warren and Liberman, 1989a). One possible explanation of this is that MOC fibers act on OHCs through the Type II neural network, particularly in the apical part of the cochlea.

With this view, the increased ΔSFOAEs from ipsilateral elicitors in the *Ipsi-Greater* frequency region may be due to an interactive combination of the effects of MOC fibers acting directly on OHCs, the effects of MOC fibers acting through the Type II neural network, and/or cochlear intrinsic effects possibly mediated by the Type II neural network. With present knowledge, it is not possible to sort out the relative contribution of each of these. Furthermore, the interaction between MOC fibers and the Type II neural network may be so strong that it does not make sense to talk about separate contributions. It will take considerably more evidence before this hypothesis can be accepted. The efferent-like synapses from type II fibers onto OHCs may have an entirely different effect on OHCs than the MOC synapses on OHCs (e.g. see Maison et al., 2008). It is clear from the anatomy, however, that the MOC efferents and the auditory-nerve type-II-fiber system are intimately intertwined and their physiological effects must be highly interrelated (Francis & Nadol, 1993; Sato et al., 1997; Thiers et al., 2000; 2002).

Ipsilateral versus contralateral effects across probe-frequency regions

The original question to be explored in this work was whether the ratio of ipsilateral to contralateral MOC effect varies across probe-frequency regions. No matter how the data are looked at, the answer appears to be that there is little variation across probe frequencies in the strengths of the ipsilateral versus the contralateral effects. Considering elicitors whose frequency content was remote from the probe frequency (where the ΔSFOAEs are most clearly due to the action of MOC efferents), there was no significant difference between the effects produced by ipsilateral versus contralateral elicitors and this was true for all probe frequency regions. For elicitors at the probe frequency, ipsilateral elicitors produced greater ΔSFOAE magnitudes than contralateral elicitors, from twice more for half-octave noise elicitors, to three times more for tone elicitors. However, there was no statistically significant difference across probe frequency in the effects of elicitors at the probe frequency. Thus, overall, the results indicate that there were no significant differences in ipsilateral compared to contralateral ΔSFOAE magnitudes obtained at different probe frequencies. Thus, the ipsilateral / contralateral ratio does not seem to vary across cochlear frequency regions in humans. It is not possible to determine the ratio of ipsilateral to contralateral MOC innervation in humans, because that requires an invasive experiment. Our results indicate that if there are anatomical differences in the ratio of ipsilateral to contralateral MOC fibers along the length of the human cochlea, the pattern of MOC activity produced centrally equalizes MOC effects across cochlear frequency regions.

Comparison with previous results

There are no previous results, from humans or animals, that provide a good comparison with our results on the cochlear effects produced by ipsilateral versus contralateral sound elicitors. There are, however, some psychophysical results that may be relevant. In various human psychophysical studies, the threshold for detecting a signal in the presence of a simultaneous noise masker has been reported to be elevated when the signal is presented shortly after the onset of the masker, compared to a presentation in the temporal center of the noise. This phenomenon, commonly known as psychophysical 'overshoot' or the 'temporal effect', has been suggested to be related to short-term neural adaptation (Green, 1969; Bacon and Viemeister, 1985) and/or the dynamic decompression of the basilar membrane input-output function as a result of efferent activation (von Klitzing and Kohlrausch, 1994). The observation that overshoot seems to be largest when the masker bandwidth is greater than one critical band (Zwicker, 1965) and that the threshold at masker onset can be reduced even if the spectral energy of a preceding noise burst to the masker is remote from the signal frequency, as in the case of notched-noise (Carlyon, 1987; McFadden, 1989) have led to a hypothesis that two different mechanisms - an on-frequency effect and an off-frequency effect - are involved in the reduction of detection threshold (Carlyon, 1987). It is suggested that the on-frequency effect may be the result of simple adaptation of the auditory nerve. Our data suggests that the on-frequency effect may also involve whatever mechanism causes the ΔSFOAE *Ipsi-Greater* effect. On the other hand, the off-frequency effect of detection threshold reduction has been hypothesized to have 'enhancement' effects such that a notched noise emphasizes the frequency region of the notch which leads to an improvement in signal detectability. An alternative explanation of the off-frequency effect is that it involves activation of MOC activity by the masker. The increased audibility of the late-presented probe would then be in agreement with known efferent gain reduction performance from animal studies where the MOC activity inhibits response to the background noise, thereby reducing auditory nerve firing adaptation and allowing the transient tone (signal) to produce a larger response that is more discriminable (Kawase et al. 1993).

V. Conclusion

The magnitude of ΔSFOAE was significantly greater when produced by ipsilateral as compared to contralateral elicitors *only* for elicitors that were close in frequency to the probe frequency. If, as past work indicates, ΔSFOAEs are produced only by MOC effects, the data indicate this *Ipsi-Greater* response is due to increased MOC activation by ipsilateral elicitors close in frequency to the probe frequency. In addition, the pattern of ΔSFOAE effects from ipsilateral versus contralateral elicitors did not appear to vary across the cochlear frequency regions that were probed. Both of these results would suggest that the relative ipsilateral/contralateral reflex strength in humans is influenced more by central processing than by the relative anatomical fiber count of the ipsilateral and contralateral MOC efferent fibers along the cochlea. However, an alternate explanation is that the *Ipsi-Greater* response is due to cochlear intrinsic factors affected by the elicitor. A viable hypothesis is that all of the observed ΔSFOAEs are due to the combined action of MOC fibers and type II auditory-nerve fibers which form an interacting neural network under, and forming synapses with, outer hair cells.

VI. Reference

Bacon, S.P., and Viemeister, N.F. (1985). 'Temporal modulation transfer functions in normal-hearing and hearing-impaired listeners,' Audiology, 24: 117-134.

Backus, B.C., Guinan, J.J., Jr. 2006. Time course of the human medial olivocochlear reflex. J Acoust Soc Am 119, 2889-2904.

Backus, B.C. and Guinan, J.J. Jr. (2007). 'Measurement of the distribution of Medial olivocochlear acoustic reflex strengths across normal hearing individuals via otoacoustic emissions,' J. Assoc Res. Otolaryngol. 8(4): 484-496.

Backus, B.C. (2007). 'Bias due to noise in otoacoustic emission measurements,' J Acoust Soc Am 121(3):1588-1603.

Carlyon, R.P. (1987). 'A release from masking by continuous, random, notched noise,' J. Acoust. Soc. Am. 81:418-426.

de Boer, E. (1996). 'Mechanics of the cochlea: Modeling efforts,' In: Dallos P.J., Popper A.N., Fay, R.R. (eds.), The Cochlea. New York: Springer-Verlag, pp.258-317.

Francis, H. W., and Nadol, J., J.B. (1993). Patterns of innervation of outer hair cells in a chimpanzee: I. Afferent endings and reciprocal synapses. *Hearing Research 64*, 184-190

Gifford, M.L., Guinan, J.J., Jr. 1987. Effects of electrical stimulation of medial olivocochlear neurons on ipsilateral and contralateral cochlear responses. Hearing Res. 29, 179-194.

Giraud, A.L., Collet, L., Chery-Croze, S., Magnan, J., Chays, A. 1995. Evidence of a medial olivocochlear involvement in contralateral suppression of otoacoustic emissions in humans. Brain Res 705, 15-23.

Green, D.M. (1969). 'Masking with continuous and pulsed sinusoids,' J. Acoust. Soc. Am. 46:939-946.

Guinan, J.J., Jr. 1990. Changes in stimulus frequency otoacoustic emissions produced by two-tone suppression and efferent stimulation in cats. In: Dallos, P., Geisler, C.D., Matthews, J.W., Steele, C.R., (Eds.), Mechanics and Biophysics of Hearing. Springer Verlag, Madison, Wisconsin. pp. 170-177.

Guinan J.J. Jr. (1996). 'The physiology of olivocochlear efferents,' In: Dallos P.J., Popper A.N., Fay, R.R. (eds.), The Cochlea. New York: Springer-Verlag, pp.435-502.

Guinan, J.J., Jr., Gifford, M.L. 1988. Effects of electrical stimulation of efferent olivocochlear neurons on cat auditory-nerve fibers. I. Rate-level functions. Hearing Res. 33, 97-114.

Guinan, J.J., Jr. , Gifford, M.L. 1988c. Effects of electrical stimulation of efferent olivocochlear neurons on cat auditory-nerve fibers. III. Tuning curves and thresholds at CF. Hearing Res. 37, 29-46.

Guinan, J.J. Jr., Warr, W.B., and Norris, B.E. (1984). 'Tonotopic organization of the olivocochlear projections from lateral and medial zones of the superior olivary complex,' J. Comp. Neurol. 226: 21-27.

Guinan, J.J. Jr., Backus, B.C., Lilaonitkul, W., Aharonson V. (2003). 'Medial olivocochlear efferent reflex in humans: Otoacoustic emission (OAE) measurement issues and advantages of stimulus frequency OAEs', J. Assoc Res. Otolaryngol. 4(4):521-540.

Kawase, T., Delgutte, B., Liberman, M.C. (1993). 'Anti-masking effects of the olivocochlear reflex, II: Enhancement of auditory-nerve response to masked tones,' J. Neurophysiol. 70: 2533-2549.

Kujawa, S.G., Liberman, M.C. 2001. Effects of olivocochlear feedback on distortion product otoacoustic emissions in guinea pig. J Assoc Res Otolaryngol 2, 268-78.

Liberman, M.C. (1988). 'Response properties of cochlear efferent neurons: monaural vs. binaural stimulation and the effects of noise,' J Neurophysiol 60:1779-1798.

Liberman, M.C., Brown, M.C. (1986). 'Physiology and anatomy of single olivocochlear neurons in cat,' Hear Res, 24:17-36

Liberman, M.C., Puria, S., Guinan, J.J., Jr. 1996. The ipsilaterally evoked olivocochlear reflex causes rapid adaptation of the 2f1-f2 distortion product otoacoustic emission. J. Acoust. Soc. Am. 99, 3572-3584.

McFadden, D. (1989). 'Spectral differences in the ability of temporal gaps in noise to reset the mechanisms underlying overshoot,' J. Acoust. Soc. Am. 85: 254-261.

Maison, S., Gassmann, M., Holstein, G.R., Bettler, B., Liberman, M.C. (2008). GABA$_{B1}$ receptors in cochlear neurons: effects of targeted deletion suggest modulation of outer hair cell function by type-II afferent fibers. (in prep)

Maison, S., Micheyl, C., Andeol, G., Gallego, S., Collet, L. (2000). 'Activation of olivocochlear efferent system in humans: influence of stimulus bandwidth,' Hear Res 140:111-125.

Meric, C. and Collet, L. (1994). 'Attention and otoacoustic emissions: a review,' Neurosci. Biobehavior. Rev. 18, 215-222.

Russell, I.J., Murugasu, E. (1998). 'Efferent suppression of basilar membrane vibration depends on tone frequency and level: implications for the active control of basilar membrane mechanics,' In: Palmer, A.R., Rees A., Summerfield A.Q., Meddis R., editors, Psychophysical and Physiological Advances in Hearing. London: Whurr Publishers Ltd; 1998. pp.19-25.

Sato, S., Henson, M., and Smith, D. W. (1997). Synaptic specialization associated with the outer hair cells of the Japanese macaque. *Hearing Research 108*, 46-54

Shera, C.A., Guinan, J.J., Jr. 1999. Evoked otoacoustic emissions arise by two fundamentally different mechanisms: A taxonomy for mammalian OAEs. J. Acoust. Soc. Am. 105, 782-798.

Sridhar, T.S., Brown, M.C., Sewell, W.F. 1997. Unique post-synaptic signaling at the hair cell efferent synapse permits calcium to evoke changes on two different time scales. J. Neurosci 17, 428-437.

Thiers, F. A., Burgess, B. J., and Nadol, J. B., Jr. (2000). Prevalence and ultrastructural morphology of axosomatic synapses on spiral ganglion cells in humans of different ages. *Hear Res 150*, 119-131.

Thiers, F. A., Burgess, B. J., and Nadol, J. B. (2002). Reciprocal innervation of outer hair cells in a human infant. *J Assoc Res Otolaryngol 3*, 269-278Von Klitzing, R., and Kohlrausch, A. (1994). 'Effect of masker level on overshoot in running and frozen-noise maskers,' J. Acoust. Soc. Am. 95, 2192-2201.

Warren, E.H., III, Liberman, M.C. 1989a. Effects of contralateral sound on auditory-nerve responses. I. Contributions of cochlear efferents. Hearing Res. 37, 89-104.

Warren, E.H., III, Liberman, M.C. 1989b. Effects of contralateral sound on auditory-nerve responses. II. Dependence on stimulus variables. Hearing Res. 37, 105-122.

Zwicker, E. (1965). 'Temporal effects in simultaneous masking and loudness,' J. Acoust. Soc. Am.38: 132-141.

Chapter 6: Binaural Summation of Medial Olivocochlear Reflex in Humans

Abstract

In this chapter the binaural summation of the medial olivocochlear (MOC) reflex was explored in humans, with the intention of determining the extent to which bilaterally presented sounds produce bigger or smaller effects than the sum of the effects of the sounds presented separately to the ipsilateral and contralateral ears. The MOC effect was quantified as the vector difference between the SFOAEs in the presence and absence of a 60 dB SPL elicitor. SFOAEs were evoked with 40 dB SPL probe tones near 0.5, 1 and 4 kHz. The elicitors: (1) had different bandwidths centered at the probe frequency or two octaves below the probe frequency, or (2) were tones or half-octave-band noise at various frequencies relative to the probe frequency. As an index of binaural summation, we used the "*Fractional Difference*" defined as the magnitude of the vector difference between the actual bilateral MOC effect and the vector summation of the ipsilateral and contralateral MOC effects. We found that for 0.5 kHz probes, the bilateral MOC effect was well predicted by the combined ipsilateral and contralateral effects so that the *Fractional Difference* not significantly different from zero for any elicitor paradigm. For 1 kHz probes, significant positive *Fractional Differences* (i.e. binaural facilitations) were produced by wide probe-centered noise elicitors (≥ 4 octaves) but not with tones, half-octave bands of noise, or off-frequency noise bands. For 4 kHz probes, significant *Fractional Differences* were observed with BBN and off-probe noisebands 1 to 2 octaves in bandwidth. In summary, for most stimuli, bilateral elicitors produced the same effect as the sum of the effects of the contralateral and ipsilateral elicitors presented separately. However, for a few stimulus conditions, all involving wide bands of noise, there was binaural facilitation. This binaural facilitation could have been produced centrally or in the cochlea.

Abbreviations

BBN	Broadband Noise Elicitor	**SFOAE$_{C}$**	Contralateral SFOAE$_{MOC}$
MEM	Middle-Ear Muscle	**SFOAE$_{I+C}$**	SFOAE$_{MOC}$ from Binaural Summation
MOC	Medial Olivocochlear	**SFOAE$_{MOC}$**	Remaining Stimulus Frequency Otoacoustic Emission
OAE	Otoacoustic Emission	**ΔSFOAE$_{Bi}$**	Bilateral MOC-Induced Change in SFOAE
SFOAE	Stimulus Frequency Otoacoustic Emission	**ΔSFOAE$_{C}$**	Contralateral MOC-Induced Change in SFOAE
SFOAE$_{Bi}$	Bilateral SFOAE$_{MOC}$	**ΔSFOAE$_{I}$**	Ipsilateral MOC-Induced Change in SFOAE
SFOAE$_{I}$	Ipsilateral SFOAE$_{MOC}$	**ΔSFOAE$_{I+C}$**	Binaural Summation (ΔSFOAE$_{C}$ + ΔSFOAE$_{C}$)

I. Introduction

The medial olivocochlear (MOC) reflex is one of the several feedback circuits that control the input to the auditory system (For a review see Guinan, 1996). The MOC reflex is binaurally organized so that the reflex can be activated ipsilaterally, contralaterally or bilaterally. Several roles in audition have been proposed for the MOC reflex – enhancement of dynamic range and/or improvement of signal to noise in the auditory periphery (Geisler 1974; Winslow and Sachs, 1998; Kawase et. al., 1993, etc.), sensory gating to mediate selective attention (e.g. Meric and Collet, 1994), and protection of the ear from acoustic overexposure (e.g. Reiter and Liberman, 1995). However, all of these roles can be performed with a monaural reflex in each ear. It is therefore unclear what the advantages of having a binaurally organized MOC reflex system are.

Results from most human studies on the MOC system had been limited to investigating only the contralateral acoustic reflex in order to avoid the effect of two-tone suppression of the probe by an elicitor presented ipsilaterally. There are, however, a few studies that measured MOC effects by the change in otoacoustic emissions produced by contralateral, ipsilateral and bilateral elicitors using the post-elicitor window technique. The early studies of this kind are difficult to interpret because the sounds they used to evoke the otoacoustic emissions also must have unintentionally elicited considerable MOC activity and it is not clear whether the additional MOC activity intentionally elicited by the broad-band-noise elicitors added in a linear way, or not (Berlin et al., 1995; Philibert et al., 1998). This problem was avoided in more recent work by measuring stimulus frequency otoacoustic emissions (SFOAEs) from low-level (40 dB SPL) tones (Backus, 2005; Backus and Guinan, 2006). These found no significant MOC binaural summation near 1 kHz in response to broadband-noise elicitors (Backus, 2005) or notched-noise elicitors (Backus and Guinan, 2007). In both cases, the magnitude of the change in the SFOAE, ΔSFOAE, produced by bilateral elicitors was well approximated by the magnitude of the complex sum of the ΔSFOAEs produced by ipsilateral and contralateral elicitors. As these studies only reported data for probes at 1 kHz, it is unclear if the absence of binaural summation would be observed at other probe frequencies or with elicitors of different bandwidths. Moreover, these previous studies only compared the magnitude of the MOC reflex while the phase information was omitted. Therefore, any binaural summation effects that might have resulted in a phase difference between the bilateral MOC reflex and the complex sum of the ipsilateral and contralateral MOC reflex would have been missed.

In this study, binaural summation of the MOC reflex in humans near 0.5, 1 and 4 kHz was systematically investigated for different elicitor frequency components. Specifically, the effects of elicitor bandwidth as well as the effects of elicitor frequency of tone and narrowband noise elicitors were explored. Analysis was done on both the magnitude and phase of the reflex and the effects on the magnitude and phase of the SFOAE vector was also quantified for the bilateral MOC reflex and the summed effects of the ipsilateral and contralateral reflexes. Results show that binaural summation enhancement could take place around the 1 and 4 kHz probe region when the response was activated by wide noisebands - indicating the importance of the medial efferent's binaural organization for its role in audition under such hearing conditions.

II. Methods

A. Subjects

All subjects included in this study had clinically normal hearing thresholds in both ears (within 20 dB re. ANSI pure tone threshold from 250 Hz to 4 kHz). Measurements were conducted in a sound-proof room. A warning light was automatically turned on before each stimulus presentation and the subject was instructed to sit still during the time that the light was on and sounds were presented. Subjects were rejected from the study if 1) the subject's middle-ear muscle (MEM) contractions were significant at the stimulus levels used for the experiments (See MEM-test in section E), 2) the subject was unable to remain awake and sit still during the experiment, or 3) the subject did not return to complete the study. A minimum SNR criterion of 3 (~9.5 dB) was applied to each data set to minimize amplitude estimation bias resulting from low SNR (Backus, 2007). This minimum SNR criterion was set to avoid significant amplitude estimation biases resulting from low SNR (Backus, 2007). The 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. The number of ears and subjects involved in this study are summarized in table 1.

Probe Frequency Region	Experiment Type	Subjects Included		Number of Ears	Age Range (Years)	Average Age (Years)
		Male	Female			
0.5 kHz	Swept-tone	1	4	8	22-31	24.4
	Swept-half-octave-noise	1	4	8	22-31	24.4
	BW	1	2	5	22-35	27
	OCBW	-	-	-	-	-
1.0 kHz	Swept-tone	3	4	11	22-33	27.5
	Swept-half-octave-noise	3	4	11	22-23	27.5
	BW	4	4	10	21-28	24.6
	OCBW	2	3	6	21-25	23.2
4.0 kHz	Swept-Tone	0	3	3	22-40	28
	Swept-half-octave-noise	1	6	7	22-40	28
	BW	1	4	6	21-32	23.6
	OCBW	0	3	3	22-35	27

Table 1: Summary of subject gender, subject age and the number of subjects included in the study. *Swept-Tone* and *Swept-half-octave-noise* refer to experiments in which the elicitor frequencies of tones, or half-octave noise bands, were varied relative to the probe frequency. *BW* refers to experiments in which the elicitor bandwidth was varied, for noise bands centered at the probe frequency. *OCBW* refers to experiments in which the elicitor bandwidth was varied, for noise bands centered 2 octaves below the probe frequency.

B. Acoustic Stimuli

As a probe sound to evoke SFOAEs in both ears, a 40-dB SPL continuous tone[22] selected at a frequency within ±10% of 0.5, 1 or 4 kHz was presented bilaterally through the earphones of 2 Etymotic ER10C acoustic assemblies. For each subject, a probe frequency was selected that: (1) was at least 100 Hz away from any spontaneous OAE with magnitude above -10 dB SPL (this was done to avoid possible entrainment – van Dijk, et al., 1988), and (2) produced the largest ΔSFOAE magnitude to a 60 dB SPL, contralateral broad-band noise (so that the signal/noise ratio (SNR) criteria could be reached with the smallest number of stimulus repeats).

To elicit MOC activity, a 60 dB SPL noise band was presented ipsilaterally, contralaterally or bilaterally for 2.5 s. Preceding the elicitor was a 0.5 s onset period from which the baseline response was measured, and following the elicitor was a 2 s period for recovery. The resulting stimulus repetition period was 5 s (Fig. 1A). Three types of experiments were done. Details of these experiments can be found in sections B1, B2 and B3. In each experiment elicitors were presented in a randomized order to avoid bias.

The baseline SFOAE (the SFOAE preceding the MOC elicitor) was measured from the vectorial difference of the ear-canal sound pressure from the 40 dB SPL probe tone with and without a 60 dB SPL suppressor tone at 110 Hz below the probe frequency[23]. The baseline SFOAE vector was measured separately from the induced-change in SFOAE in runs in which the suppressor was presented for 0.5 s every 1 s (Fig. 1B). For both suppressor-tones and MOC-elicitors, 5-ms rise/fall cosine ramps were introduced at the presentation edges to minimize spectral splatter. Consecutive elicitor or suppressor presentations had opposite polarities so that upon averaging their acoustic waveforms would cancel leaving a residual measure equal to the amount of induced change in the SFOAE vector.

Calibrations of the acoustic output from the two sound sources in each ER10C acoustic assembly were done (using the microphone in the ER10C) at the beginning of every data gathering session and frequently within a session. Noise bursts were made to be spectrally flat by applying these calibrations.

B1. Experiment 1: Bandwidth series (BW)

Noise-band elicitors with the probe frequency as their logarithmic center frequency were used to elicit MOC effects. The elicitor bandwidths used in this study included: (1) 0.5, 1, 2, 4 octave noise bands and broadband noise (BBN) (0.1-10kHz) for the 0.5 and 1 kHz probes and (2) 0.5, 1, 2 octave noise bands and BBN for the 4 kHz probe.

B2. Experiment 2: Off-centered bandwidth series (OCBW)

Noise-band elicitors with bandwidths of 0.5, 1, 1.5 and 2 octaves centered at 2 octaves below the probe frequency were used to elicit MOC effects. Preliminary studies showed that these off-centered elicitor noise bands did not induce significant two-tone suppression (Appendix of Chapter 4).

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[22] Contralateral tones at the probe frequency presented at 40 dB SPL were found to be weak elicitors of efferent response (Guinan et al., 2003).

[23] Backus and Guinan (2007) found that the SFOAE obtained using these parameter values can underestimate the true SFOAE amplitude, i.e. the suppressor produces only 80-100% suppression. The variability in the *degree* of underestimation could have increased the standard error of our group averages. However, underestimation of the SFOAE magnitude did not affect the shape of the MOC effect curves because, for a given ear, all points were normalized by the same SFOAE measure.

B3. Experiment 3: Tone or half-octave-noise swept frequency series

Tone or half-octave noise band elicitors (60 dB SPL) were presented in half-octave steps at elicitor frequencies from 2 octaves below to 2 octaves above the 0.5 kHz probe, 2.5 octaves below to 2.5 octaves above the 1 kHz probe, or from -3.5 octaves below to 1 octave above the 4 kHz probe.

C. Measurement Analysis

Responses were rejected as being contaminated with artifacts when the difference between one pair of responses and the next pair exceeded a criterion. Stimulus pairs were used because elicitors (or suppressors) were alternated in polarity across stimulus repetitions. Multiple response pairs were vectorially averaged to achieve response averages with $N \geq 12$ stimulus repetitions. The averaged waveforms were then heterodyned to obtain the complex waveform of the response at the probe frequency. Details of the heterodyning method and specification of the frequency domain filtering can be found elsewhere (Guinan et al, 2003).

The complex amplitude of the ear canal sound pressure at the probe frequency, P(t), is the sum of the probe-tone and the evoked SFOAE(t) complex amplitude. An MOC elicitor, or a suppressor, can induce a change in the SFOAE and thereby change P(t). Changes in the SFOAE(t), ΔSFOAE(t), were calculated from P(t) by the vectorial difference between P(t) and P_{baseline} where P_{baseline} is the vector average of P(t) between 50-450 ms, i.e. the average P(t) before the onset of the suppressor or MOC elicitor (see Guinan 2003 for more detail). The MOC-induced change was then expressed as a fraction of the SFOAE by dividing ΔSFOAE(t) by the baseline SFOAE vector. That is,

$$\Delta\mathrm{SFOAEn(t)} = \frac{\mathrm{P(t)} - \mathrm{P_{Baseline}}}{\mathrm{SFOAE}} = \frac{\Delta\mathrm{SFOAE}}{\mathrm{SFOAE}} \qquad \text{(eq. 1)}$$

where,
$\mathrm{P(t)}$ = the complex heterodyned measurement, and $0 < t < 5$s.
$\mathrm{P_{Baseline}}$ = the vectorial average of P(t), and $0.05 < t < 0.45$s
SFOAE = the complex baseline stimulus frequency otoacoustic emission evoked by the probe tone.
ΔSFOAEn(t) = the change in the SFOAE normalized by the baseline SFOAE.

In the above, SFOAE(t) and ΔSFOAE(t) were the raw, un-normalized values and ΔSFOAEn(t) was the normalized value. In all of the remaining, we will use only the normalized values and will drop the "n" so that henceforth ΔSFOAE(t) = ΔSFOAEn(t) of above.

Normalized ΔSFOAE(t) data were vectorially averaged in either a 0.4 s "during-elicitor" time window ending 0.05 s before the end of the elicitor (for contralateral ΔSFOAE(t)), or a 0.1 s "post-elicitor" time window starting at 0.05 s after the end of the elicitor (for ipsilateral and bilateral Δ SFOAE(t) and, for comparison, contralateral ΔSFOAE(t)). Averaging in the post-elicitor window avoids two-tone-suppression effects of the probe that can be evoked by ipsilateral and bilateral elicitors, but at the expense of capturing the MOC effect during its decay. Two-tone-suppression is absent for contralateral elicitors so the contralateral ΔSFOAE(t) can be averaged from a during-elicitor window near the end of the elicitor presentation which allows us to capture the maximum MOC effect elicited. The noise floor estimate was obtained from averaging the ΔSFOAE(t) in a time-window of the same duration as the (during or post-elicitor) data-analysis time window, but positioned such that the end of the noise time window was 50 ms before the end of a stimulus repetition period.

The change in the SFOAE produced by MOC activity was considered as the SFOAE obtained during MOC inhibition, $\mathrm{SFOAE_{MOC}}$, also shown in Figure 2. With the two measured quantities being the SFOAE and the ΔSFOAE vectors, $\mathrm{SFOAE_{MOC}}$ was calculated as:

$$\mathrm{SFOAE_{MOC}} = \frac{\mathrm{SFOAE} - \Delta\mathrm{SFOAE}}{\mathrm{SFOAE}} = \frac{A_{\mathrm{SFOAE_{MOC}}} e^{i\theta_{\mathrm{SFOAE_{MOC}}}}}{A_{\mathrm{SFOAE}} e^{i\theta_{\mathrm{SFOAE}}}} = \frac{A_{\mathrm{SFOAE_{MOC}}}}{A_{\mathrm{SFOAE}}} e^{i(\theta_{\mathrm{SFOAE_{MOC}}} - \theta_{\mathrm{SFOAE}})} \qquad \text{(eq. 2)}$$

In eq. 2 above, ΔSFOAE is the value of ΔSFOAE before it was normalized by the SFOAE magnitude (throughout the rest of the text, ΔSFOAE refers to the normalized ΔSFOAE). This equation for $\mathrm{SFOAE_{MOC}}$ includes normalizing by the magnitude of the original SFOAE magnitude, and referencing the phase of $\mathrm{SFOAE_{MOC}}$ to the phase of the original SFOAE.

D. Quantification of Binaural Summation

Binaural summation was quantified by the "Fractional Difference" which was calculated in the following steps: (1) ΔSFOAEI+C was calculated from the vector sum of ΔSFOAEI and ΔSFOAEC (see Fig. 2B). (2) SFOAEI+C was calculated as in equation 1, with I+C substituted for MOC (see Fig. 2B). (3) The Fractional Difference was calculated as the difference between SFOAEBi magnitude (the SFOAEMOC from a bilateral elicitor) and SFOAEI+C magnitude (the SFOAEMOC from binaural summation, see Fig. 2) as a fraction of the SFOAEI+C magnitude. That is:

$$\text{Fractional Difference} = \frac{|SFOAE_{Bi}| - |SFOAE_{I+C}|}{|SFOAE_{I+C}|} \qquad \text{(eq. 3)}$$

The Fractional Difference shown in the plots was obtained by first calculating the Fractional Difference separately for each subject and then averaging the values across subjects. With the above definition, a positive (negative) Fractional Difference corresponds to binaural facilitation (occlusion). In addition, we also analyzed the phase as the difference between the phases of SFOAEBi elicited by bilateral activation versus the phase of SFOAEI+C from binaural summation.

E. Middle-ear-muscle (MEM) contraction test

A MEM test was performed on each subject to ensure that the MEMs were not activated at the stimulus levels used. In this test, a 65 dB SPL continuous suppressor tone at 110 Hz above the probe frequency was presented in addition to the normal acoustic stimuli. With this paradigm, only MEM contractions produce a change in the sound pressure at the SFOAE probe frequency. Thus, 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. Details of the experimental rational can be found in the Methods section of Chapter 2.

F. Determining the statistical significance of variations across parameters

To determine the statistical significance of the variations of MOC effect 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 MOC effect results passed the Lillifores test for normality. If they did not pass, the Friedman non-parametric two-way ANOVA was used. Statistical significance was accepted at the 0.05 level. The data were compared to a control data set that measured the response under the Null-hypothesis of no MOC effect. The control data were the noise floor measurements taken from a time-window of the same duration as the (during or post-elicitor) data-analysis time window, but positioned such that the end of the noise time window was 50 ms before the end of a stimulus repetition period.

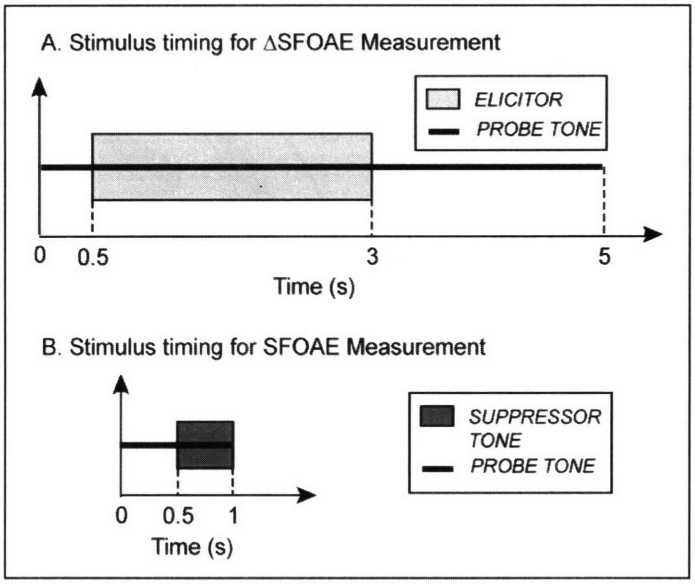

Figure 1. Temporal presentation of stimuli. A. For the measurement of the elicitor-induced ΔSFOAE, there was an initial delay of 0.5 s to establish the baseline response, then a 2.5 s tone or noise burst to elicit MOC activity, followed by a 2 s recovery period. This stimulus pattern was repeated every 5 s with the polarity of the elicitor alternated so that upon averaging the measurements, the elicitors would cancel leaving a residual pressure equal to elicitor-induced ΔSFOAE. **B**. For the SFOAE measurement, there was an initial delay of 0.5 s to establish the baseline response, then a 0.5 s suppressor tone at 110 Hz below the probe frequency. This stimulus pattern was repeated every 1 s with the polarity of the suppressor alternated.

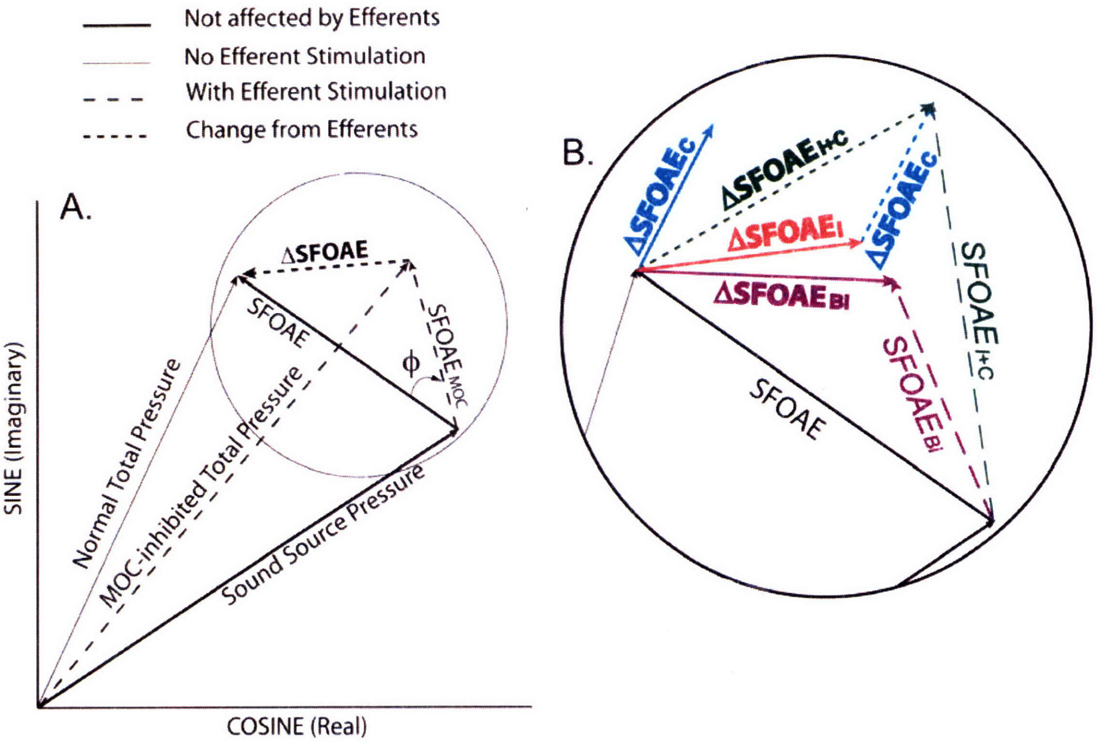

Figure 2. A. Vector diagram of MOC effects on sound pressures in the ear canal. The arrows are vectors in the complex plane such that the length of the arrow represents the magnitude and the direction of the arrow represents the phase. Before MOC stimulation, the *Sound Source Pressure* and the SFOAE summate to form the *Normal Total Pressure* in the ear canal. In the presence of an MOC effect, the SFOAE magnitude and phase are changed as shown by SFOAE$_{MOC}$ resulting in a new ear-canal sound pressure (*MOC-inhibited Total Pressure*). The change in the ear canal pressure shows the resulting change in the SFOAE, ΔSFOAE. Note that the angle ϕ shows the phase delay of SFOAE$_{MOC}$ from the SFOAE phase, opposite the sign convention used in the other figures. **B. Vector diagram depicting the relationship between ipsilateral (red), contralateral (blue), bilateral (purple) and the 'Binaural-Sum' (green) ΔSFOAE (bold) and SFOAE$_{MOC}$ (italics).** Note that the 'Binaural-Sum' ΔSFOAE is the vectorial sum of the ipsilaterally and contralaterally-elicited ΔSFOAEs. The Binaural-Sum SFOAE$_{MOC}$ (SFOAE$_{I+C}$) is the vectorial difference between the SFOAE and the Binaural-Sum ΔSFOAE.

II. Results

In this study, we measured the changes in SFOAEs elicited by various sounds with a view toward determining the extent to which bilaterally presented sounds produce bigger or smaller effects than the sum of the effects of the same sounds presented separately to the ipsilateral and contralateral ears. The comparison of amplitudes was done by the "*Fractional Difference*" and the comparison of phase by a simple phase difference. *Fractional Difference* was quantified from the vector difference between SFOAE_{Bi}, the SFOAE present during the action of a bilateral elicitor, and $\Delta\text{SFOAE}_{\text{I+C}}$, a calculated SFOAEMOC value that sums the effects produced by the actions of ipsilateral and contralateral elicitors presented separately (see Methods). The term SFOAEMOC will be used to denote the SFOAE that remains after the inhibition produced by an elicitor (i.e. the ΔSFOAE), as shown in Fig. 2. So SFOAE_{Bi}, $\Delta\text{SFOAE}_{\text{I}}$, $\Delta\text{SFOAE}_{\text{C}}$, and $\Delta\text{SFOAE}_{\text{I+C}}$, are each a SFOAEMOC, with each calculated from a corresponding change vector, a ΔSFOAE (Fig. 2).

In the first half of this study, binaural summation as a function of elicitor bandwidth was explored. Elicitor bandwidths were systematically varied for elicitor noise bands centered at the probe frequency (Results Section A) or 2 octaves below the probe frequency (Results Section B). In the second half of this study, we investigate binaural summation as a function of elicitor frequency with elicitors that were either tones or half-octave noisebands (half-octave-noise) (Results Section C).

Preliminary studies were carried out on each subject to determine if the stimulus levels used in this study induced significant MEM-contractions that would confound the measurement of MOC effects. All data included in this study were from subjects that did not show significant MEM-contractions in response to the acoustic stimuli used here. Hence, induced changes in the SFOAE originate from within the cochlea, presumably due to MOC efferent activity (see Discussion).

A. Magnitude and phase of SFOAE_{Bi} and $\text{SFOAE}_{\text{I+C}}$ as functions of elicitor bandwidth centered at the probe frequency

The magnitudes and phases of the SFOAEMOC'S resulting from bilateral activation and binaural summation are shown in Figures 2, 3 and 4 (left panels) for probe frequencies of 0.5, 1 and 4 kHz, respectively. In general, bilateral activation and binaural summation both produced SFOAE magnitude inhibition and phase advances. The right side of each figure shows the resulting *Fractional Differences* and the SFOAEMOC phase differences.

For the 0.5 kHz Probe, the SFOAEMOC magnitudes from binaural summation were greater than from bilateral activation for most elicitor bandwidths (Fig. 3A). However, because of significant inter-ear variation, as seen from the relatively large error bars, the Fractional Difference (Fig. 3B) was not a significant function of elicitor bandwidth (ANOVA: $P_{0.5\text{kHz}} = 0.53$). The SFOAEMOC phases near 0.5 kHz generally increased with increasing elicitor bandwidth (Fig. 3C), but also showed large standard errors of the mean (error bars) and the difference between the SFOAEMOC phases did not vary significantly with elicitor bandwidth (ANOVA: $P=0.47$) nor were any phase differences significant (Fig. 3D).

For the 1 kHz Probe, more SFOAEMOC magnitude inhibition was produced by bilateral activation than by binaural summation especially for wider noise bands (Fig. 4A). The *Fractional Difference* decreased significantly with increasing elicitor bandwidth (ANOVA: $P_{1\text{kHz}} < 0.001$) and was significantly negative for 4-octave and broad-band noise (BBN) elicitors. A negative *Fractional Difference* implies more inhibition by bilateral activation than by the summation of the monaural inhibitions. The *Fractional Differences* from the 4-octave and wide-band noise elicitors were not statistically different from each other, and their average value was approximately -0.2. This implies that the SFOAE magnitude inhibition due to wideband bilateral activation ($\geq$ 4 octaves) was approximately 20% more than the SFOAE magnitude inhibition due to binaural summation. The SFOAEMOC phase leads (Fig. 4C) from bilateral activation and binaural summation almost overlay as increasing functions of elicitor bandwidth. As a result, all SFOAEmoc phase differences (Fig. 4D) were close to zero and did not vary significantly with elicitor bandwidth (ANOVA: P=0.17).

For the 4 kHz Probe, the SFOAEMOC magnitudes from bilateral activation and binaural summation were approximately equal (Fig. 5A) and the resulting *Fractional Difference* (Fig. 5B) was close to zero and did not vary significantly with elicitor bandwidth (ANOVA: 0.64). The SFOAEMOC phase leads (Fig. 5C) were greater for bilateral activation especially with the BBN elicitor. Thus the SFOAEMOC phase differences varied significantly with elicitor bandwidth (ANOVA: P=0.003) such that with BBN elicitors, bilateral activation produced a greater phase lead that binaural summation by approximately 3 degrees and this was statistically significant.

B. Magnitude and phase of $SFOAE_{Bi}$ and $SFOAE_{I+C}$ as functions of elicitor bandwidth at 2 octaves below the probe frequency

Figures 6 and 7 show the SFOAEMOC magnitudes and phases for 1 and 4 kHz probes as functions elicitor bandwidth for noise bands centered two octaves below the probe frequency. Near 1 kHz, SFOAEMOC magnitudes and phases from bilateral activation and binaural summation were approximately equal (Fig. 6A, C). The *Fractional Differences* and the phase differences were close to zero and did not vary significantly with elicitor bandwidth (Fig. 6B, C) (ANOVA: P=0.70 and P=0.56, respectively).

For the 4 kHz Probe, both the magnitude inhibition and the phase advance increased as functions of elicitor bandwidth (Figs. 7A and 7C). Bilateral activation produced smaller SFOAEMOC magnitudes than binaural summation for all elicitor bandwidths (Fig. 7 A). The *Fractional Differences* varied significantly with elicitor bandwidths (ANOVA: P=0.02) and were negative for all elicitor bandwidths implying more SFOAE magnitude inhibition from bilateral activation (Fig. 7B). Bilaterally-induced SFOAEMOC phase leads were also greater that those from binaural summation (Fig. 7C). The differences in SFOAEMOC phases varied significantly with elicitor bandwidth (ANOVA: P<0.001) such that the difference became increasingly positive with increasing elicitor bandwidth (Fig. 7D).

C. Magnitude and phase of $SFOAE_{Bi}$ and $SFOAE_{I+C}$ as functions of elicitor frequency

Figure 8 shows results for 1 kHz probes from half-octave noise elicitors of various frequencies relative to the probe frequency. The figure layout is the same as in previous figures. The SFOAEMOC magnitudes from both bilateral activation and binaural summation, as functions of elicitor frequency, overlay almost exactly (Fig. 8A). The smallest SFOAEMOC magnitude (i.e. the greatest SFOAE magnitude inhibition) was observed for elicitor frequencies centered at the probe frequency. The functions then decreased gradually with increasing difference between the elicitor and probe frequencies such that almost no difference in the magnitude inhibition was observed for noise bands at frequencies remote from the probe frequency. The *Fractional Difference* (Fig. 8B) was close to zero for all elicitor frequencies and did not vary significantly with elicitor frequency (ANOVA: P=0.14). The SFOAEMOC phase patterns from bilateral activation and binaural summation were also remarkably similar and showed more phase lead for elicitor frequencies below the probe frequency (Fig. 8C). The differences in SFOAE phase leads were close to zero for all elicitor frequencies, did not vary significantly with elicitor frequency (ANOVA: P=0.72) (Fig. 8D).

Similar results showing no significant differences between the SFOAEMOC magnitudes or phases from bilateral activation versus binaural summation were found for all probe frequencies and both half-octave noise-band elicitors (Fig. 9) and tone elicitors (Fig. 10). In all cases, the *Fractional Differences* and phase differences did not vary significantly with elicitor frequency (ANOVA: P>0.05; individual P values shown in Figs 9 and 10) and the values were not statistically different from zero.

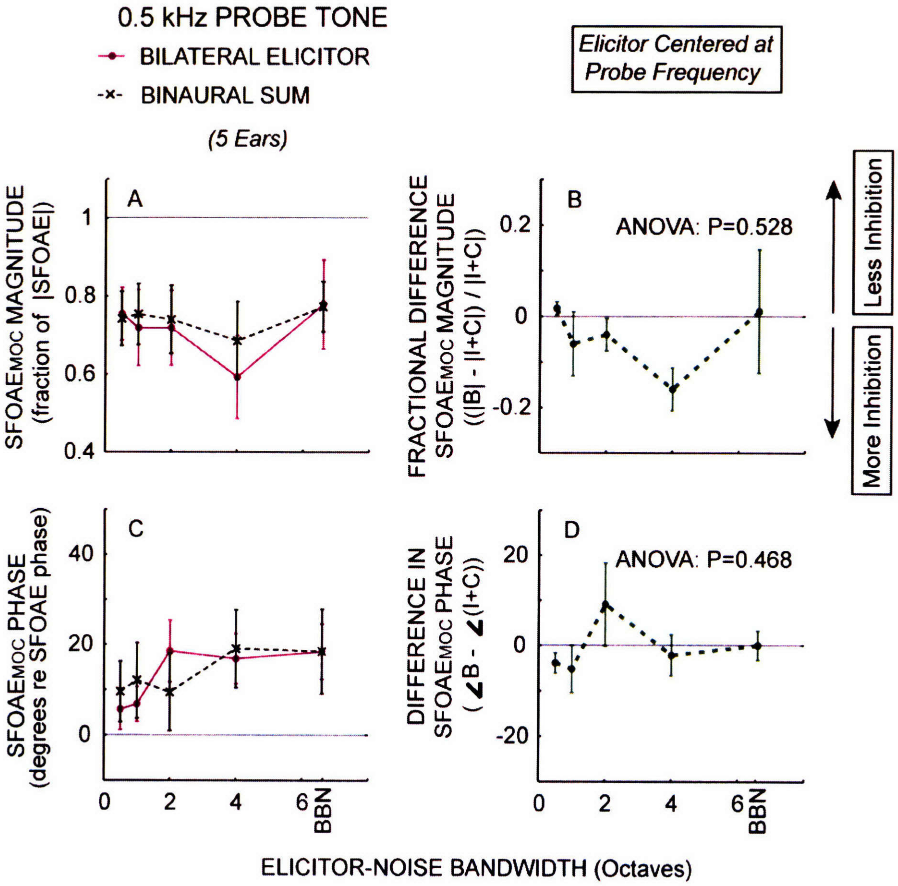

Figure 3. Comparison of the magnitude (top) and phase (bottom) between SFOAE_{Bi} (purple ●) and $\text{SFOAE}_{\text{I+C}}$ (black: X) as a function of elicitor bandwidth. Corresponding Fractional Differences are in the right panel (green: dashed lines). Elicitors were centered at the 0.5 kHz probe frequency. Error bars represent 1 standard error of the mean. Right: Significance of the *Fractional Difference* (B) and the Phase Difference (D) from zero are marked with asterisks: '*' (P≤0.05), '**' (P≤0.01), '***' (P≤0.001). Right Column y-axis label: 'B' = SFOAE_{Bi}; '(I+C)' = $\text{SFOAE}_{\text{I+C}}$.

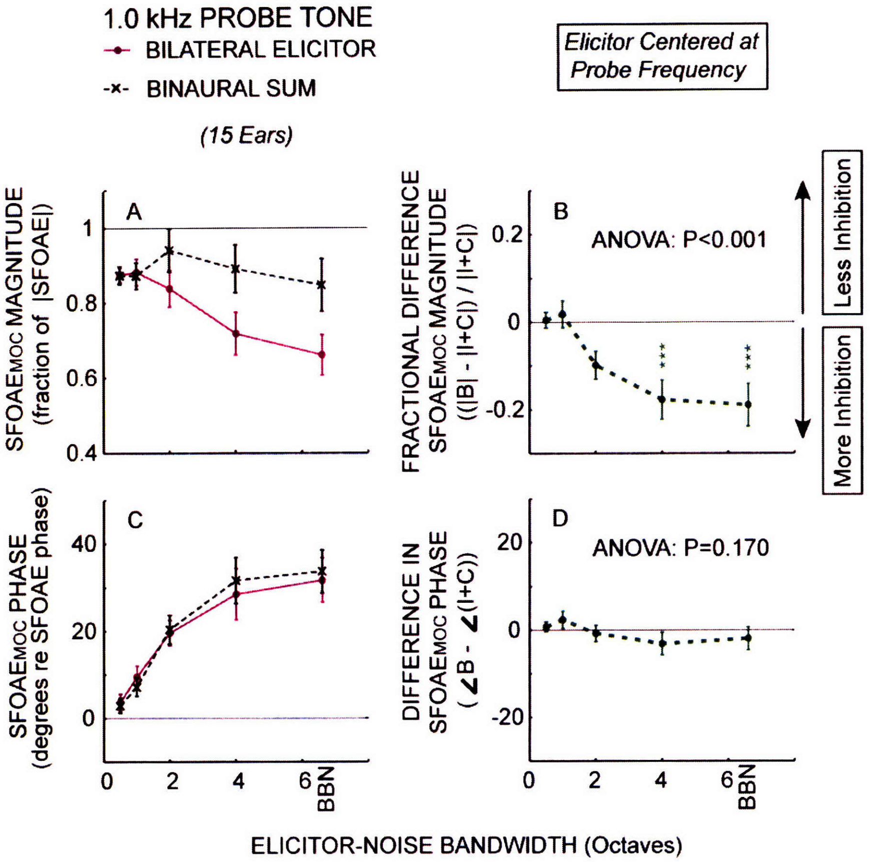

Figure 4. Comparison of the magnitude (top) and phase (bottom) between SFOAE$_{Bi}$ (purple) and SFOAE$_{I+C}$ (black) as a function of elicitor bandwidth. Corresponding Fractional Differences are in the right panel (green: dashed lines). Elicitors were centered at the 1 kHz probe frequency. Error bars represent 1 standard error of the mean. Right: Significance of the *Fractional Difference* (B) and the Phase Difference (D) from zero are marked with asterisks: '*' ($P \leq 0.05$), '**' ($P \leq 0.01$), '***' ($P \leq 0.001$). Right Column y-axis label: 'B' = SFOAE$_{Bi}$; '(I+C)' = SFOAE$_{I+C}$.

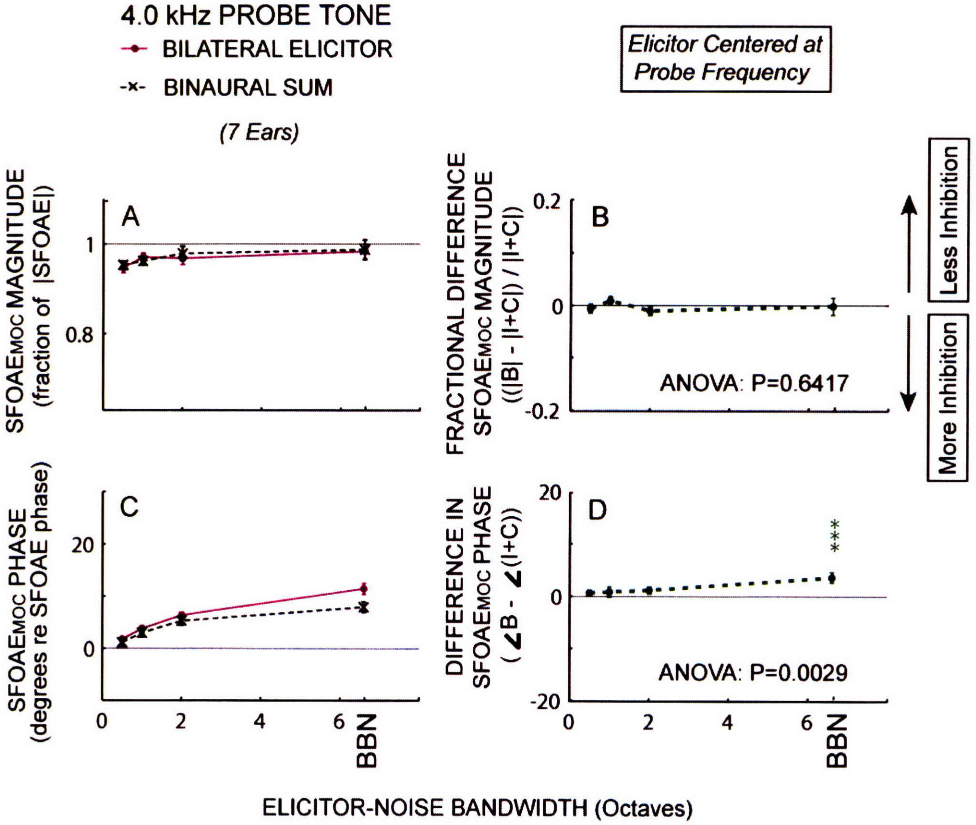

Figure 5. Comparison of the magnitude (top) and phase (bottom) between SFOAE_{Bi} (purple) and $\text{SFOAE}_{\text{I+C}}$ (black) as a function of elicitor bandwidth. Corresponding Fractional Differences are in the right panel (green: dashed lines). Elicitors were centered at the 4 kHz probe frequency. Error bars represent 1 standard error of the mean. Right: Significance of the *Fractional Difference* (B) and the Phase Difference (D) from zero are marked with asterisks: '*' ($P \leq 0.05$), '**' ($P \leq 0.01$), '***' ($P \leq 0.001$). Right Column y-axis label: 'B' = SFOAE_{Bi}; '(I+C)' = $\text{SFOAE}_{\text{I+C}}$.

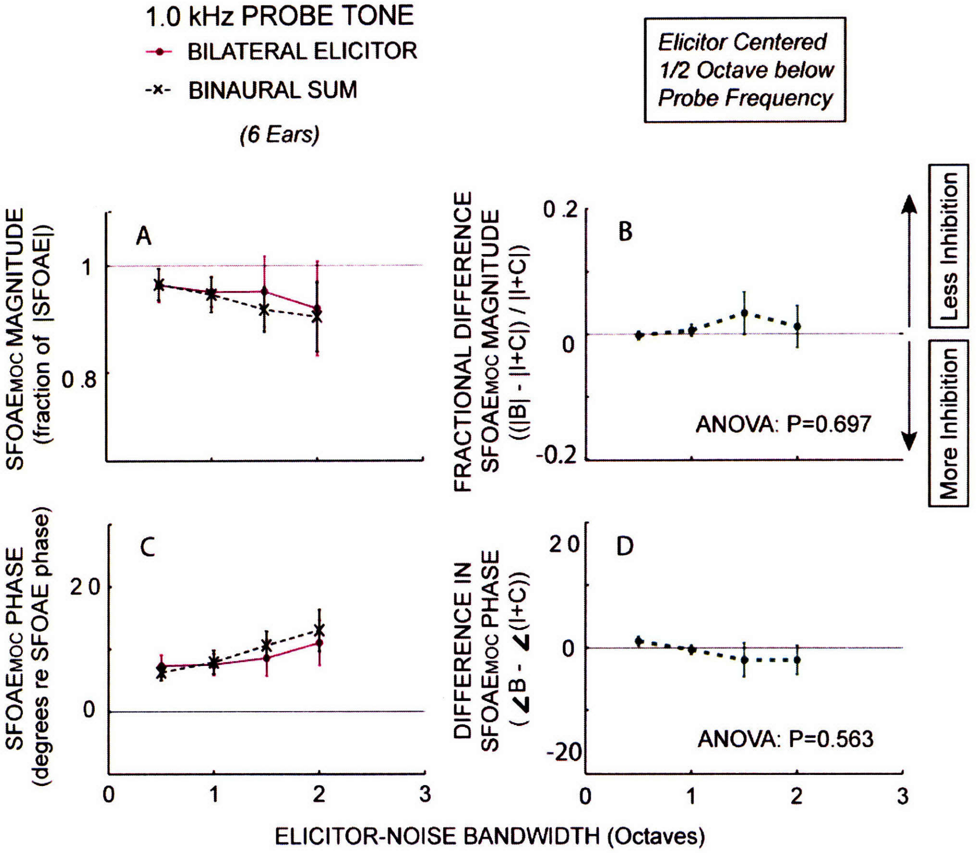

Figure 6. Comparison of the magnitude (top) and phase (bottom) between SFOAE$_{Bi}$ (purple) and SFOAE$_{I+C}$ (black) as a function of elicitor bandwidth. Corresponding Fractional Differences are in the right panel (green: dashed lines). Elicitors were centered at 2 octaves below the 1 kHz probe frequency. Error bars represent 1 standard error of the mean. Right: Significance of the *Fractional Difference* (B) and the Phase Difference (D) from zero are marked with asterisks: '*' ($P \leq 0.05$), '**' ($P \leq 0.01$), '***' ($P \leq 0.001$). Right Column y-axis label: 'B' = SFOAE$_{Bi}$; '(I+C)' = SFOAE$_{I+C}$.

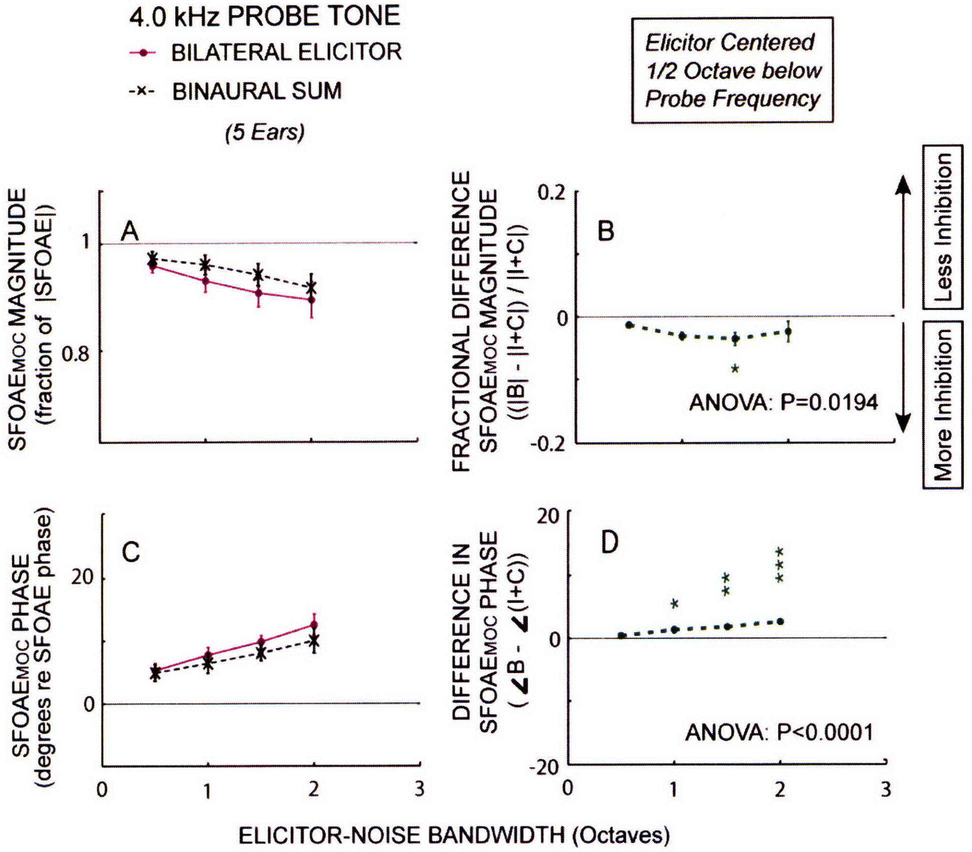

Figure 7. Comparison of the magnitude (top) and phase (bottom) between SFOAE$_{Bi}$ (purple) and SFOAE$_{I+C}$ (black) as a function of elicitor bandwidth. Corresponding Fractional Differences are in the right panel (green: dashed lines). Elicitors were centered at 2 octaves below the 4 kHz probe frequency. Error bars represent 1 standard error of the mean. Right: Significance of the *Fractional Difference* (B) and the Phase Difference (D) from zero are marked with asterisks: '*' ($P \leq 0.05$), '**' ($P \leq 0.01$), '***' ($P \leq 0.001$). Right Column y-axis label: 'B' = SFOAE$_{Bi}$; '(I+C)' = SFOAE$_{I+C}$.

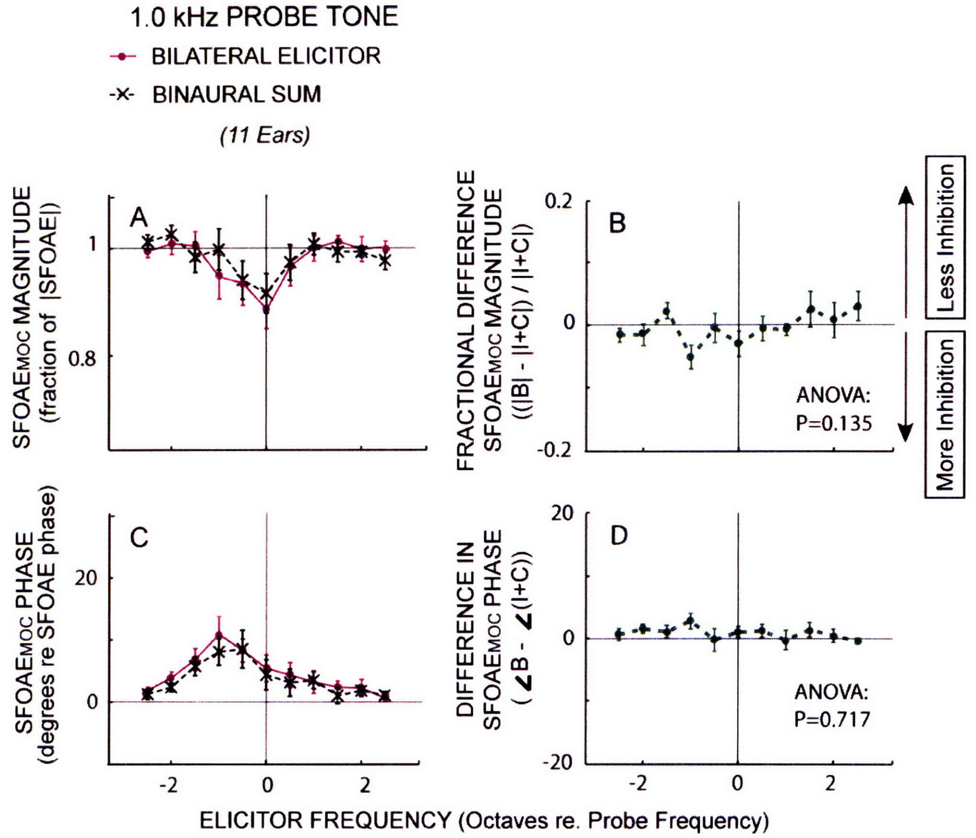

Figure 8. Comparison of the magnitude (top) and phase (bottom) between SFOAE$_{Bi}$ (purple) and SFOAE$_{I+C}$ (black) as a function of tone elicitor frequency. Corresponding Fractional Differences are in the right panel (green: dashed lines). Error bars represent 1 standard error of the mean. Right: Significance of the *Fractional Difference* (B) and the Phase Difference (D) from zero are marked with asterisks: '*' ($P \leq 0.05$), '**' ($P \leq 0.01$), '***' ($P \leq 0.001$). Right Column y-axis label: 'B' = SFOAE$_{Bi}$; '(I+C)' = SFOAE$_{I+C}$.

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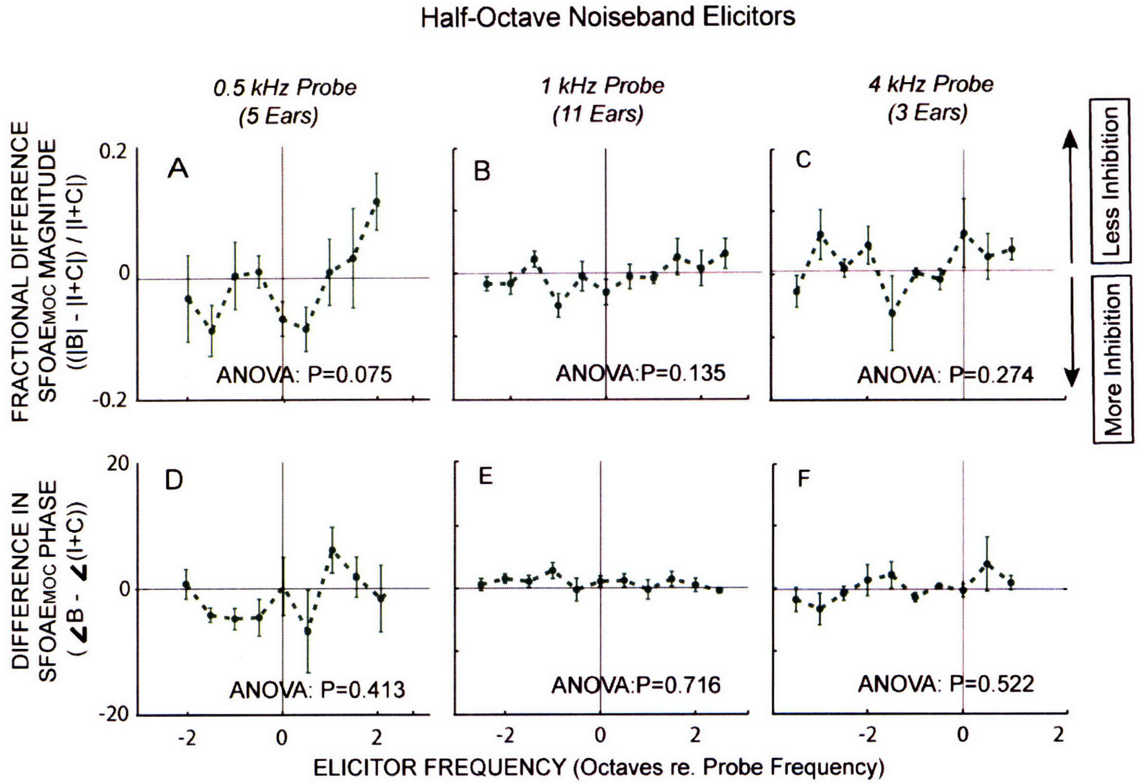

Figure 9. Fractional Difference (top) and Phase Difference (bottom) as a function of tone elicitor frequency. Error bars represent 1 standard error of the mean. Significance of the *Fractional Difference* (top) and the Phase Difference (bottom) from zero are marked with asterisks: '*' ($P \leq 0.05$), '**' ($P \leq 0.01$), '***' ($P \leq 0.001$). y-axis label: 'B' = $SFOAE_{Bi}$; '(I+C)' = $SFOAE_{I+C}$.

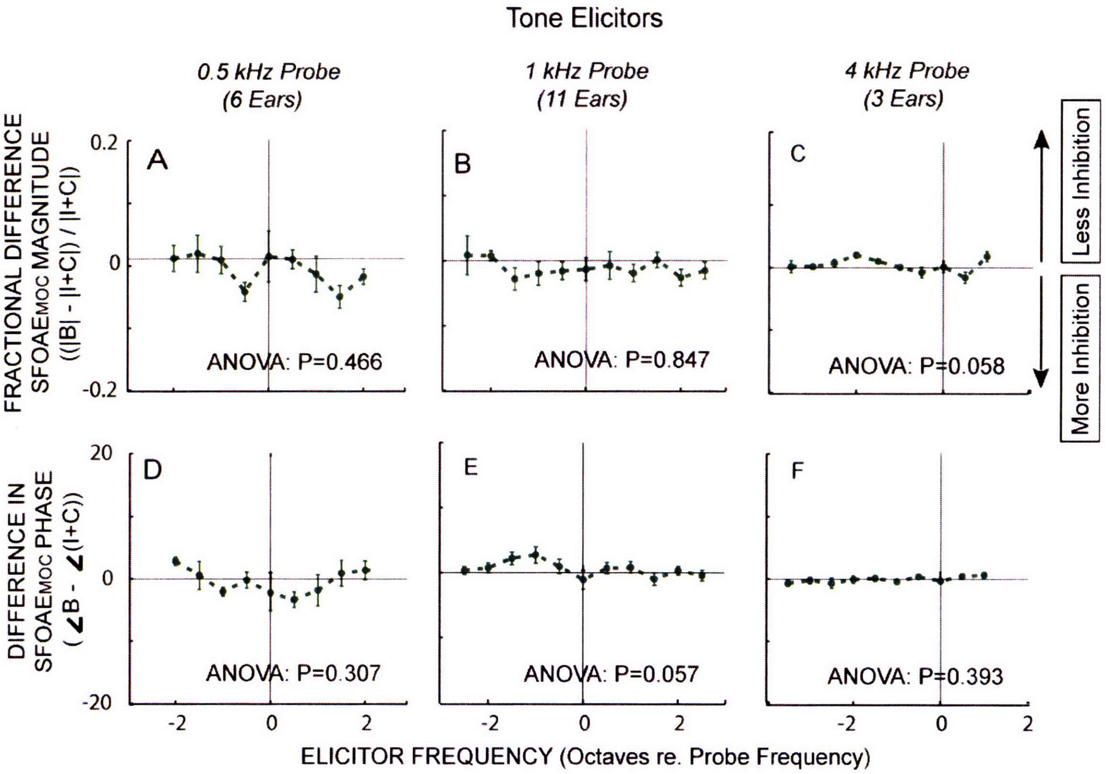

Figure 10. Fractional Difference (top) and Phase Difference (bottom) as a function of half-octave-noise elicitor frequency. Error bars represent 1 standard error of the mean. Significance of the *Fractional Difference* (top) and the Phase Difference (bottom) from zero are marked with asterisks: '*' ($P \leq 0.05$), '**' ($P \leq 0.01$), '***' ($P \leq 0.001$). y-axis label: 'B' = $SFOAE_{Bi}$; '(I+C)' = $SFOAE_{I+C}$.

IV. Discussion

Data and Methods Considerations

To investigate for the presence or absence of binaural facilitation/occlusion, we compared the bilateral effects and the calculated binaurally-summed effects as seen in the amount of SFOAE magnitude inhibition. A significantly negative (or positive) *Fractional Difference* in the inhibited SFOAEMOC magnitude was taken to signify binaural facilitation (or occlusion). In addition, the phase difference between the SFOAEMOC phases during bilateral activation and binaural summation was analyzed.

Of greatest concern is the data quality near 0.5 kHz which was not as good as the data near 1 or 4 kHz. This can be seen from the larger error bars in the 0.5 kHz data. The variance in the data can be broken down into variance in the data due to background noise and variance due to inter-subject differences. Effects of inter-subject variation can be reduced with an increased subject pool. Background noise, which is mostly microphone noise, increases as frequency decreases and thus affects the 0.5 kHz data more than at the other two probe frequencies for a given number of experimental repeats. Moreover, the variance of our measure, the *Fractional Difference* is inherently greater than the variance of each of the variables used for its calculation. Hence, improvement of data quality by increasing the measurement repeats and the subject pool size might yield significant results and more insight at 0.5 kHz.

In Chapter 5, we discussed the possibility that in addition to MOC effects, cochlear intrinsic effects may significantly contribute to the elicitor-induced changes in SFOAEs for ipsilateral elicitors near the probe frequency. Since significant negative *Fractional Differences* were observed for some wide-band elicitors but never for tone or half-octave-noise elicitors centered at the probe frequencies, it is more likely that the binaural facilitation observed is related to MOC effects and not to cochlear intrinsic effects. Moreover, that significant binaural facilitation was observed for wide noise band elicitors but not for any tone or half-octave-noise elicitors suggest that binaural facilitation requires wide spatial summation that include cochlear regions remote from the probe frequency. Moreover, since binaural facilitation at 1 kHz was significant with 4-octave and BBN elicitors, but not with noisebands centered 2 octaves below the probe, suggests that regions basal to the 1 kHz probe contributed more to the binaural facilitation. At 4 kHz, that significant binaural facilitation was observed with noisebands centered 2 octaves below the probe but not with the BBN perhaps because the energy provided by the BBN over the frequency regions of the off-centered noisebands was insufficient to produce significant binaural facilitation. Hence binaural facilitation appears to be a complex function of probe frequency and elicitor frequency in relation to the probe frequency and elicitor level. This binaural facilitation could have been produced centrally or in the cochlea.

Another notable feature in our data is that near 4 kHz, a significantly greater SFOAEmoc phase lead could be elicited by the bilateral MOC effects than by the calculated binaurally-summed MOC effects for BBN elicitor and the wider noisebands centered at 2 octaves below the probe. Greater phase leads were not observed with narrowband elicitors or tones which suggest that the under-lying mechanism also relies on spatial recruitment of MOC effects remote from the cochlear region of the probe frequency and over regions wider than ½ octave in cochlear space.

Comparison to previous studies

Most previous studies on the MOC acoustic reflex in humans only focused on the contralateral effects to avoid confounding effects of two-tone suppression by the presence of an ipsilateral elicitor of nearby frequency to the probe. Only 3 previous human study included a comparison between bilateral and binaural summation of the acoustic MOC reflexes (Berlin, et al., 1995; Philibert, et al., 1998; Backus, 2005; Backus and Guinan, 2006).

In the first study (Berlin, et al., 1995), MOC effects were quantified as the change in click-evoked otoacoustic emissions in the presence and absence of 65 dB SPL white noise presented ipsilaterally, contralaterally or bilaterally. The authors reported the presence of binaural occlusion. However, to evoke the OAEs in this study, 80 dB and 90 dB clicks were used. At these click levels, it is almost certain that both significant MEM-contractions and probe-induced MOC effects (by the clicks) would take place (Guinan, et al. 2003). Thus it is difficult to interpret the Berlin et al. results.

The second study, by Philibert, et al. (1998), quantified the MOC effects by the suppressive effects of ipsilateral, contralateral and bilateral BBN elicitors on transient-evoked OAE (TEOAE) magnitudes. Their Figure 1 showed that average MOC effects were approximately 1.8 dB, 1.6 dB and 2.3 dB attenuations of the TEOAEs produced by BBN elicitors presented ipsilaterally, contralaterally and bilaterally. The sum of the ipsilaterally-elicited and contralaterally-elicited attenuations is 3.4 dB which is greater than the 2.3 dB bilaterally-elicited attenuation, implying binaural occlusion. However, their transient-evoked OAEs were from clicks between 60 and 72 dB SPL, levels high enough to pose the same methodological issues high enough for the probe to evoke MOC effects which cloud the interpretation of the data.

The Backus (2005) & Backus and Guinan (2006) studies employed SFOAEs evoked by tones near 1 kHz. MOC effects were quantified by the same ΔSFOAE metric as in this current study. The elicitors used were BBN (Backus, 2005) or a notched-noise elicitor (Backus and Guinan, 2006) (2.1 octave spectral notch centered at the probe-tone frequency). The 40 dB SPL probe level and 60 dB SPL elicitor level were identical to ours. However, these studies only compared the magnitudes of ΔSFOAEs for bilateral elicitors and binaural summation without analysis of the ΔSFOAE phase information. Using BBN elicitors, the bilaterally-elicited ΔSFOAE did not show significant facilitation or occlusion over the binaurally-summed ΔSFOAE. However, using notch-noise elicitors, binaural occlusion was observed in one subject while in the other 2 subjects, the bilaterally-elicited ΔSFOAEs were approximately equal to the binaurally-summed ΔSFOAEs. The differences in the outcome of their study versus ours stem from the fact that these previous studies only used the magnitudes of ΔSFOAE where as we used both the magnitude and phase. Hence, any differences in the ΔSFOAE phases would be missed by these previous studies.

V. Conclusion

Our results show that, for most stimuli, bilateral elicitors produced the same effect as the sum of the effects of the contralateral and ipsilateral elicitors presented separately. However, for a few stimulus conditions, all involving wide bands of noise, there was binaural facilitation. This binaural facilitation could have been produced centrally or in the cochlea.

VI. Reference

Backus, B.C. (2005). 'Using Stimulus Frequency Otoacoustic Emissions to study basic properties of the human medial olivocochlear reflex,' Ph.D. Thesis, MIT, Chapter 2: 12-18.

Backus, B.C. and Guinan, J.J. Jr. (2006). 'Time-course of human medial olivocochlear reflex,' J. Acoust. Soc. Am. 119(5Pt1): 2889-2904.

Backus, B.C. (2007). 'Bias due to noise in otoacoustic emission measurements,' J Acoust Soc Am 121(3):1588-1603.

Berlin, C.I., Hood, L.J., Hurley, A., Wen, H., Kemp, D.T. 1995. Binaural noise suppresses linear click-evoked otoacoustic emissions more than ipsilateral or contralateral noise. Hearing Res. 87, 6-103.

Geisler, C.D. (1974). 'Hypothesis on the function of the crossed olivocochlear bundle,' J. Acoust. Soc. Am. 56: 1908-1909.

Guinan J.J. Jr. (1996). 'The physiology of olivocochlear efferents,' In: Dallos P.J., Popper A.N., Fay, R.R. (eds.), The Cochlea. New York: Springer-Verlag, pp.435-502.

Guinan, J.J. Jr., Backus, B.C., Lilaonitkul, W., Aharonson V. (2003). 'Medial olivocochlear efferent reflex in humans: Otoacoustic emission (OAE) measurement issues and advantages of stimulus frequency OAEs', J. Assoc Res. Otolaryngol. 4(4):521-540.

Kawase, T., Delgutte, B., Liberman, M.C. (1993). 'Anti-masking effects of the olivocochlear reflex, II: Enhancement of auditory-nerve response to masked tones,' J. Neurophysiol. 70: 2533-2549.

Meric, C. and Collet, L. (1994). 'Attention and otoacoustic emissions: a review,' Neurosci. Biobehavior. Rev. 18, 215-222.

Philibert, B., Veuillet, E., Collet, L. 1998. Functional asymmetries of crossed and uncrossed medial olivocochlear efferent pathways in humans. Neurosci Lett 253, 99-102.

Reiter, E.R. and Liberman, M.C. (1995). 'Efferent-mediated protection from acoustic overexposure: Relation to slow effects" of olivocochlear stimulation,' J. Neurophys. 73: 506-514.

Winslow, R.L. and Sachs, M.B. (1988). 'Single tone intensity discrimination based on auditory nerve rate responses in backgrounds of quiet, noise and with stimulation of crossed olivocochlear bundle,' Hear Res 35: 165-190.

Chapter 7: Summary & Future Directions

I. Thesis Review

Medial olivocochlear efferents form a descending neural feedback circuit that allows for gain control of the cochlear amplifier by the central nervous system. During acoustic stimulation, MOC efferents alter the properties of the electro-motile outer hair cells (OHC) resulting in a reduction in the gain of both the cochlear amplifier and the mechanical stimulus to the inner hair cells. Despite the vast body of knowledge on Medial Olivocochlear (MOC) efferent anatomy and physiology, many aspects of the system's inner workings and the functional roles of the MOC efferents remain uncertain. A variety of evidence indicates that the brain controls the gain of the cochlear amplifier in a frequency specific manner although the degree of frequency specificity is poorly understood. The goal of this thesis was to investigate the MOC acoustic reflex's tuning properties for different cochlear frequency regions and with different MOC elicitor lateralities and elicitor frequency contents. Knowing the reflex tuning properties should give insight into, and put constraints on, the role of MOC efferents in hearing.

Our main focus on was on the frequency dependences of the human MOC system as determined by measurements of MOC-induced changes in SFOAEs as functions of elicitor frequency, laterality, and frequency content for 3 probe frequencies (Chapters 2, 3 and 4). There were two secondary focuses (1) The relative strengths of the ipsilateral and contralateral MOC effect at different regions along the cochlea (Chapter 5), and (2) binaural facilitation as a function of probe and elicitor frequency (Chapter 6)

Our findings show that the MOC system has both frequency specific effects and integration over a wide frequency range. The data also suggest that efferent effects induced by elicitors near the probe frequency may be fundamentally different from the effects induced by off-frequency elicitors, which raises important questions on theories of auditory gain control. On the whole, the findings are consistent with the hypothesis that efferents may improve signal detection in background noise. The following sections give a summary of the conclusions from each study as well as suggested future directions for research.

II. Chapter Conclusions & Future Directions

Chapter 2: The Frequency Dependences of Contralateral, Ipsilateral and Bilateral Medial-Olivocochlear-Efferent Acoustic Reflexes in Humans

Summary

This chapter quantified 1) the MOC effects in the cochlear frequency region near 1 kHz as a function of elicitor frequency and elicitor laterality using both tone and narrow-band-noise elicitors and 2) the sharpness of MOC-effect tuning curves (TC). The results show that human MOC-effect SFOAE-based TCs near response threshold levels were sharper than MOC efferent neural tuning in cats and guinea pigs. The TCs were V-shaped and had tips that were always displaced from the probe frequency, commonly towards lower frequencies . However, the data from Chapter 3 indicates that the tip frequency depends on the metric used (i.e. if TCs were made from $|SFOAE_{MOC}|$, they would be centered at the probe frequency). For mid-level elicitors (60 dB SPL), human MOC effects were less frequency selective and exhibited a skew in the response pattern such that elicitors at frequencies below the probe frequency were usually most effective at eliciting ΔSFOAEs. The finding that there is generally larger efferent effects for elicitors in frequency regions below the probe frequency, is consistent with an anti-masking role for efferents to combat the upward-spread of masking.

Future Directions of Research

Several functional roles of the MOC system in audition have been suggested. One hypothetical role involves the enhancement of signal detection in the presence of background masking noise. Studies have shown that during auditory attention tasks, efferents can be activated at the frequency of the attended sound, presumably to improve detection performance (Maison et al., 2001). If this is true, then as efferents are stimulated with noise, our ability to detect signals should improve during the course of efferent response build-up over time. If such masked-threshold shifts are due, at least in part, to the MOC efferents, then there should be a positive correlation in the size of the threshold shifts and the MOC efferent response across variations in signal and noise parameters as well as across subjects. To see if this is the case, the strength of the MOC reflex elicited by an ipsilateral notched-noise masker could be measured concurrently with the masked-threshold at different times during the course of the masker. The MOC reflex strength could be measured by the ΔSFOAE and the masked-threshold with traditional psychophysical methods.

Chapter 3: The Frequency Dependences of the Contralateral, Ipsilateral and Bilateral Medial-Olivocochlear-Efferent Acoustic Reflexes in Humans as Functions of Probe Frequency

Summary

This study investigated the frequency dependances of human medial olivocochlear (MOC) effects in three different probe-frequency regions, 0.5, 1 and 4 kHz. The overall change in the SFOAE produced by MOC stimulation, ΔSFOAE, varied with probe frequency, elicitor laterality, elicitor frequency and elicitor bandwidth. The largest ΔSFOAEs were for 0.5 kHz probes and the smallest for 4 kHz probes, opposite the pattern of MOC innervation, which indicates that the strength of the MOC acoustic reflex may be controlled more by central factors than by peripheral innervation. MOC effects could produce magnitude inhibition and/or phase advances in the SFOAE vector and these appeared to be separate functions of elicitor frequency. The MOC inhibition of the $\mathrm{SFOAE_{MOC}}$ magnitude was largest for on-frequency elicitors (elicitor frequencies near the probe frequency) whereas the MOC-induced change in $\mathrm{SFOAE_{MOC}}$ phase was largest for off-frequency elicitors. One hypothesis to account for this is that on-frequency elicitors predominately inhibit the probe-tone traveling wave, whereas off-frequency elicitors shift the traveling wave along the frequency axis by selectively inhibiting apical or basal parts of the traveling-wave envelope.

Future Direction for Research

In chapter 2, human MOC-effect tuning curves were measured from ΔSFOAE magnitudes. The metric for these TCs, ΔSFOAE magnitude incorporates changes in both $\mathrm{SFOAE_{MOC}}$ magnitude and phase. In Chapter 3, ΔSFOAE magnitude, $\mathrm{SFOAE_{MOC}}$ magnitude and $\mathrm{SFOAE_{MOC}}$ phase were found to be different functions of elicitor frequency. Thus, it might be useful to measure TCs for changes in $\mathrm{SFOAE_{MOC}}$ magnitude and separately for changes in $\mathrm{SFOAE_{MOC}}$ phase. For all probe frequency tested, $\mathrm{SFOAE_{MOC}}$ magnitude frequency functions were approximately V-shaped and symmetric about the probe frequency, so TCs from $\mathrm{SFOAE_{MOC}}$ magnutudes might be similar (whether the largest $\mathrm{SFOAE_{MOC}}$ magnitude at low sound levels is at the probe frequency is unknown because the SNR of the data at low levels are too poor). Also, characterization of tuning curves at the different probe frequencies would be useful.

Interpretation of tuning curves from ΔSFOAE magnitude, $\mathrm{SFOAE_{MOC}}$ magnitude or $\mathrm{SFOAE_{MOC}}$ phase requires knowledge of how these changes translate to efferent-induced changes in auditory-nerve-fiber firings. Such calibration of efferent-induced changes in SFOAEs and efferent-induced changes in neural patterns could be achieved by simultaneously measuring ΔSFOAE (as in our current metric) and changes in the auditory brainstem response (ABR) wave 1 which is due to the auditory nerve. Such information about the human MOC system's ability to inhibit cochlear output would be an important piece of the puzzle pertaining to the MOC system's functional significance.

Chapter 4: The Effect of Elicitor Bandwidth on Contralateral, Ipsilateral and Bilateral Medial Olivocochlear Efferent Acoustic Reflexes in Humans at Low, Medium and High Probe Frequencies

Summary

This study investigated the effect of elicitor bandwidth on MOC effects as quantified by ΔSFOAEs in humans. ΔSFOAEs increased as elicitor bandwidth increased regardless of whether the noise bands were centered at the probe or at an apical frequency region remote from the probe. Overall, the results indicate that, since the energy-level of the elicitors were kept constant, the spatial summation produced by recruiting MOC activity over elicitor frequency regions remote from the probe frequency was greater than the effect of reducing the spectral level of the elicitor near the probe frequency. For half-octave noise bands, the largest ΔSFOAEs were for 0.5 kHz probes and the smallest for 4 kHz probes but for wide-band noise, 0.5 and 1 kHz probes showed ΔSFOAEs of similar magnitudes. These results suggest that the strength of the MOC acoustic reflex is controlled more by central factors than by peripheral innervation. Lastly, measurements of ΔSFOAEs elicited by half-octave noise bands were used to calculate ΔSFOAE as a function of elicitor bandwidth. The calculated values were similar to the actual measured ΔSFOAEs from increasing elicitor bandwidth for contralateral elicitors, but showed a consistent over estimation for ipsilateral and bilateral elicitors. Collectively, our results reveal that sound excitation over almost the entire cochlear length of both cochleas can collectively affect the mechanical response at a specific cochlear place.

Future Direction for Research

In the study by Maison et al. (2000), the contribution to MOC effects of frequency components from narrow sub-bands along the cochlear length were calculated as the difference in MOC effect from two elicitor bandwidths (i.e. the increment in MOC effect from increasing the elicitor bandwidth was taken to be the MOC effect due to the additional elicitor bandwidth (the new sub-band). They found that the derived MOC effect as a function of elicitor frequency sub-bands exhibited a 'Mexican hat' pattern: the OAE inhibition was greatest at the probe frequency but adjacent side-bands close to but on either side of the probe frequency produced OAE enhancement. It would be of interest to explore whether this 'Mexican hat' pattern can be found in any of our SFOAE measures. To do this, we would need to repeat the swept-tone experiments at finer elicitor frequency spacing with either tone elicitors or noise bands narrower than ½ octave..

Chapter 5: Effects of Ipsilateral versus Contralateral Elicitors on Stimulus Frequency Otoacoustic Emissions as Functions of Elicitor Frequency Content

Summary

This study investigated the relative effects of ipsilateral and contralateral MOC reflexes in humans using SFOAEs as the metric of MOC effects. The results show that for 0.5, 1 and 4 kHz probe frequencies, the magnitude of ΔSFOAE was significantly greater when produced by ipsilateral as compared to contralateral elicitors *only* for elicitors that were close in frequency to the probe frequency. The difference between the ipsilateral and contralateral ΔSFOAE magnitudes diminished for broadband noise elicitors, elicitor tones with frequencies remote from the probe frequency, and noise bands centered two octaves below the probe frequency. The pattern of ΔSFOAE effects from ipsilateral versus contralateral elicitors did not appear to vary across the three cochlear frequency regions that were probed. These results may indicate that the relative ipsilateral/contralateral reflex strength in humans is influenced more by central processing than by the relative anatomical fiber count of the ipsilateral and contralateral MOC efferent fibers along the cochlea. However, it is also possible that the ΔSFOAEs close to the probe frequency may be partly due to cochlear intrinsic effects produced by the elicitor.

Future Directions for Research

It was suggested in this Chapter that ipsilateral ΔSFOAEs close to the probe frequency may be due at least in part to cochlear intrinsic effects. An example of a sound-induced intrinsic effect on an otoacoustic emission is provided by the onset adaptation of distortion-product otoacoustic emission (DPOAEs) in cats. Liberman et al. (1996) found a rapid adaptation component (time constant ~100ms, similar to typical MOC effects) which disappeared when the MOC efferents were cut, and a slow adaptation component (time constant ~1 second) that did not disappear when all of the efferents were cut, i.e. this slow adaptation was due to cochlear intrinsic effects. So one way to assess the presence of significant cochlear effects may be by estimating the time-constant of the post-elicitor change in the SFOAE due to an ipsilateral elicitor close to the probe frequency. If there are significant intrinsic effects similar to those found by Liberman et al., then the time-constant of change in the unsuppressed SFOAE might be on the order of ~1 s. On the other hand, if the effect responsible for the change in the unsuppressed SFOAE is dominated by MOC effects, then the time constant should be on the order of 100s of ms similar to typical MOC effects.

Chapter 6: Binaural Summation of Medial Olivocochlear Reflex in Humans

Summary

In this chapter the binaural summation of medial olivocochlear (MOC) reflex effects was explored in humans, with the intention of determining the extent to which bilaterally presented sounds produce bigger or smaller effects than the sum of the effects of the sounds presented separately to the ipsilateral and contralateral ears. Effects of elicitor bandwidth and elicitor frequency relative to the probe frequency were explored. Our results show that, for most stimuli, bilateral elicitors produced the same effect as the sum of the effects of the contralateral and ipsilateral elicitors presented separately. However, for a few stimulus conditions, all involving wide bands of noise, there was binaural facilitation. This binaural facilitation could have been produced centrally or in the cochlea.

Future Directions for Research

Almost all previously published reports on MOC effects in humans used probe sounds to evoke OAEs that were also potent elicitors of MOC activation, i.e. they were ipsilateral elicitors. In these papers, the MOC effect of a contralateral elicitor was determined by measuring the OAE with and without the contralateral sound. Thus these measurements are taking the difference between an OAE affected by the ipsilateral MOC reflex and an OAE affected by both the ipsilateral and contralateral MOC reflexes (i.e. the bilateral reflex, although not with identical stimuli in both ears). It would be useful to know if the contralateral effect measured in this is the same as if it were measured without the presence of an ipsilateral probe that excited ipsilateral MOC activity. To do this, one would use a paradigm similar to the one we have used, except that in place of our ipsilateral noise or tone elicitor, one would use the probe sound used in a published MOC experiment (the contralateral sound would still be a broad-band noise). If no binaural summation were found, this result would indicate that the published experiments obtained the same result that would have been obtained from measuring the contralateral reflex alone. If there was binaural summation, then these measurements would have been affected by the particular probe sound used.

III. Insights on the Role of MOC Reflex

The objective of this thesis was to quantify the frequency dependences of elicitor-induced changes in SFOAEs at different probe frequencies and for different elicitor frequency components. Knowing these dependencies should provide insights and place limits on theories for the roles of the MOC acoustic reflexes in hearing. Below are two examples of implications of our results for the role of the MOC acoustic reflexes in hearing.

1) *MOC reflex may help improve signal detection in noisy backgrounds.*
   MOC effects to mid-level elicitors (60 dB SPL) and MOC-effect TCs showed that elicitor frequencies below the probe frequency (probe ~1 kHz) were generally more potent elicitors of MOC activity (Chapter 2). That more potent elicitors of MOC effects were found for elicitors lower in frequency than the probe, a region where the growth of masking with masker level is known to be more rapid than a linear growth (upward spread of masking), is consistent with the hypothesis of a feedback anti-masking role of medial efferents. That is, noise from frequency regions that produce the most masking also evoke the most MOC activity, presumably to help combat this masking. Moreover, for mid-level elicitors the capabilities of the MOC reflex to affect a particular cochlear region is more global than frequency specific: effects to mid-level elicitors could be elicited from almost the entire cochlea (Chapters 2, 3, 4).

2) *The MOC reflex may be affecting cochlear mechanics in a more complicated manner than the concept of uniform gain reduction assumed in most cochlear models*
   With mid-level elicitors of 60 dB SPL, MOC effects were found to affect the magnitude and phase of SFOAEs as separate functions of elicitor frequency (Chapter 3). It was hypothesized that the on-frequency elicitors predominately inhibit the overall amplitude of the probe-tone traveling wave, whereas off-frequency elicitors shift the traveling wave along the frequency axis by selectively inhibiting apical or basal parts of the traveling-wave envelope. In past analyses of the effects of the cochlear amplifier on traveling waves and on SFOAEs, when cochlear amplifier gain was changed, it was considered to be a single quantity that always varied along the length of the cochlea in the same way, that is, if the gain was cut in half, it was cut in half everywhere equally (e.g. Zweig and Shera, 1995). To our knowledge, there is no model that considers changes in cochlear amplifier gain that might be biased toward the apex or the base, as might be produced by MOC activity from elicitors below or above the probe frequency. Our reasoning suggests that such frequency-selective MOC action produces more complex changes in SFOAEs than simply a reduction of SFOAE amplitude. It would be very useful if this reasoning were checked and further elucidated with results from an actual model.

   The inhibitory effects of 70 dB SPL contralateral tone elicitors on the firing rate of auditory nerve fibers in cats for units with CF near 2 kHz (Warren and Liberman, 1989b) showed: 1) MOC-inhibition of auditory nerve fibers by contralateral tones were skewed to frequencies below the probe. 2) MOC-inhibition of the auditory nerves could be elicited over roughly a 1.5 octaves below and 1 octave above the fiber's CF. These patterns from the cat strike remarkable similarities to our human |ΔSFOAE| results at 1 kHz. In chapter 3 the effects of ΔSFOAE were decomposed into the magnitude inhibition and phase lead of the $\mathrm{SFOAE_{MOC}}$. For contralateral elicitors, we found insignificant magnitude inhibitions but significant phase changes (leads) in the $\mathrm{SFOAE_{MOC}}$ so that phase changes were the dominant contributing factor to the contralateral ΔSFOAEs at 1 kHz. Presuming that the Warren and Liberman (1989b) results from anesthetized cats apply to awake humans, these results suggest that ΔSFOAE magnitudes correspond better to auditory-nerve inhibitions than $\mathrm{SFOAE_{MOC}}$ magnitudes. Although the SFOAE may be the simplest OAE and the easiest to interpret in terms of underlying changes in the cochlea, it appears that interpreting changes in SFOAEs is not simple.

III. Reference

Liberman, M. C., S. Puria, et al. (1996). "The ipsilaterally evoked olivocochlear reflex causes rapid adaptation of the 2f1-f2 distortion product otoacoustic emission." J. Acoust. Soc. Am. 99 (6): 3572-3584.

Maison, S., Micheyl, C., Andeol, G., Gallego, S., Collet, L. (2000). 'Activation of olivocochlear efferent system in humans: influence of stimulus bandwidth,' Hear Res 140:111-125.

Maison S, Micheyl C, Collet L. (2001) Influence of focused auditory attention on cochlear activity in humans. Psychophysiology. 38:35-40.

Warren, E.H., and Liberman, M.C. (1989b). 'Effects of contralateral sound on auditory nerve responses. II. Dependence on stimulus variables,' Hear Res. 37(2):105-121.

Zweig, G. and Shera, C. A. (1995). 'The origin of periodicity in the spectrum of evoked otoacoustic emissions,' J. Acoust. Soc. Am. 98(4): 2018-2047.