Using Stimulus Frequency Otoacoustic Emissions to Study Basic Properties of the Human Medial Olivocochlear Reflex

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Submitted to the Harvard-M.I.T. Division of Health Sciences and Technology in partial fulfillment of the requirements for the degree of

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THESIS ABSTRACT

The medial olivocochlear reflex (MOCR) is a brainstem-based neural feedback circuit by which mammals adaptively adjust the gain of their ears in response to changing environmental conditions. Activating the reflex with sound reduces cochlear gain, but the mechanisms by which the reflex produces its cochlear effects, the role(s) the reflex plays in hearing and many basic reflex properties are not well-understood. This thesis quantifies four basic properties of the reflex in humans using stimulus-frequency-otoacoustic-emissions (SFOAEs) that address the following issues:

(1) The relative strengths of ipsilateral and contralateral reflex pathways
(2) The reflex time-course
(3) The response of the reflex to amplitude modulated (AM) noise
(4) The distribution of reflex strengths across a normal-hearing population

Activating the reflex with ipsilateral or contralateral noise produced, on average, the same effect in cochlea at the 1 kHz place, contrary to expectations based upon animal studies. Simultaneous bilateral activation produced an effect that was equivalent to the sum of ipsilateral and contralateral activations, on average. Thus, no prevailing binaural interaction took place for our stimulus.

Activating the reflex caused detectable changes in the cochlea within 25 ms; the changes continued to develop for 100's of milliseconds. The decay rate upon reflex deactivation was generally faster than the onset rate (τ_{decay} = 159 ± 54 ms, τ_{onset} =277 ± 62 ms). In addition, our characterization of onset and decay time-courses suggested that a single second order cellular process (probably in outer hair cells) may govern the bulk of both time-courses. The reflex is not fast enough to protect the ear against loud impulse sounds such as gunshots.

Amplitude modulating a wideband noise used to activate the reflex did not, in general, produce larger effects as had been previously reported. The question of whether AM can enhance MOCR responses under some circumstances for some subjects remains unanswered. AM rates important for information in speech (2 - 11 Hz) produced a DC MOCR response. It is possible that conversational speech primes the MOCR to a level conducive to detecting speech in noise.

Inter-subject differences were found in the cochlear effects at the 1 kHz place when the MOCR was activated. One difference was a subject-specific rapid frequency variation. This finding called into question basic assumptions of how MOCR activation changes SFOAEs. Averaging across frequencies revealed a second subject-specific difference that was attributed to differences in the regional strength of the reflex (near 1 kHz) between subjects. Regional strength varied by a factor of 7 across 24 subjects. Since a strong MOCR has been shown to protect the ear against acoustic trauma in animals, otoacoustic emission-based tests of reflex strength may help predict susceptibility to acoustic trauma in humans; this study demonstrates that such tests are feasible.

The basic properties of the MOCR quantified by this thesis contribute to our understanding of the cellular mechanism that generate the reflex's effects, provides insight into the role(s) the reflex plays in hearing, and may eventually lead to clinically useful tests.

Supervisor: John J. Guinan, Ph.D.; Associate Professor of Otology and Laryngology, Harvard Medical School

Acknowledgements

At times during my doctoral work friendly people would ask, "Do you see the light at the end of the tunnel?" "Yes," I replied, "but I can also see the light from stars that are billions of light years away." I am happy to report that a Ph.D. thesis is more like a tunnel than a star.

The journey through my "tunnel" was often a lonely one, but it was not a solitary one. It cannot begin, progress, or end without help from others.

I acknowledge my thesis advisor, Dr. John J. Guinan, a dedicated scientist and gifted experimentalist. I deeply appreciated John's mentorship. He is as dedicated to developing young scientists as he is to science itself.

I acknowledge committee members: Dr. M. Charles Liberman, Dr. Christopher Shera and Dr. Garrett Stanley. Each had a strong influence on the thesis; their input was invaluable.

I acknowledge the support staff at the Massachusetts Eye and Ear Infirmary, and Dianna Sands in particular. Without Dianna, the well-oiled Eaton Peabody Laboratory would crumble into a pile of rusty screws resembling former employees.

I acknowledge my family and friends (you know who you are). Family and friends have played a central role in forming me. They have an indirect effect on this manuscript but the most significant one—they are a central force for everything I do.

We hereby give this manuscript to the body of scientific knowledge.

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Chapter 1: Overview

ABBREVIATIONS

AC	alternating current
AM	amplitude modulation
BM	basilar membrane
DC	direct current
DPOAE	distortion product otoacoustic emission
MOC	medial olivocochlear
MOCR	medial olivocochlear reflex
OAE	otoacoustic emission
SFOAE	stimulus frequency otoacoustic emission
TEOAE	transiently evoked otoacoustic emission

I. THESIS INTRODUCTION

Vertebrate animals send descending efferent input to their sensory organs through which they adjust their biological sensors to changing environmental conditions. A good example is the pupillary light reflex which contracts the iris in response to bright light. Similarly, the mammalian hearing system has neural feedback circuitry designed to control the ear's input. The medial olivocochlear reflex (MOCR) is one such auditory reflex (for a review see(Guinan 1996), but less is known about the MOCR than the pupillary light reflex because it is hidden from view. We do know that the MOCR is a sound-activated reflex and that, when activated, reduces the gain of the ear by decreasing the mechanical response of the basilar membrane (BM) to sound (Murugasu and Russell 1996; Cooper and Guinan 2003).

Currently, there is no consensus for the primary role of the MOCR in hearing. The topic has produced several postulated roles: developmental (Walsh, McGee et al. 1998), protective (Rajan and Johnstone 1983; Reiter and Liberman 1995), dynamic range adjustment (Geisler 1974; Winslow and Sachs 1988), enhancing signal detection in noise (Winslow and Sachs 1988; Kawase, Delgutte et al. 1993), and aiding selective attention (Hernandez-Peon 1956; Meric and Collet 1994). To narrow the search we need to better understand the reflex's *basic properties*—e.g. "What is the range of reflex strengths across the normal-hearing populations?", "How fast does the reflex produce its effects in the cochlea?"—and gain an appreciation for what the reflex fundamentally can and cannot do.

The discovery of otoacoustic emissions (Kemp 1978) and the ensuing discovery that those emissions can be modified by activating MOC fibers (Mountain 1980) gives us the tools needed to investigate basic properties of the MOCR non-invasively in normal-hearing humans.

We chose to use stimulus frequency otoacoustic emissions (SFOAEs) over TEOAEs and DPOAEs because they are the easiest to interpret. DPOAEs are generated by two mechanisms (Shera and Guinan 1999) and it is unclear how the MOCR interacts with each one. In the case of TEOAEs, the sound level of the clicks used to probe the cochlea has been shown to elicit MOCR activity making a 'no MOCR activation' reference difficult to measure.

The purpose of this thesis is to quantify and discuss 4 basic properties of the MOCR using stimulus frequency otoacoustic emissions (SFOAEs): (1) the relative strengths of the ipsilaterally, contralaterally, and bilaterally activated reflex, (2) the time-course of the reflex (3) the efficacy of amplitude modulation (AM) for activating the reflex and (4) the distribution of reflex strengths within a normal-hearing population. Each property was chosen to build upon an existing literature and to provide data that bear upon the role the reflex may play in hearing.

II. THESIS STRUCTURE

Thesis chapters 2-5 are self-contained papers, each designed to introduce, quantify and discuss 1 MOCR property. Chapters 1 and 6 are introduction and summary chapters.

III. CHAPTER OVERVIEWS

A. Chapter 1: Overview

This chapter includes the motivation for the thesis and an overview of thesis contents. For a review of the literature on the MOCR see Guinan 1996.

B. Chapter 2: Relative strengths of the ipsilaterally, contralaterally, and bilaterally activated medial olivocochlear reflex

This chapter quantifies the relative strengths of the ipsilateral vs. contralateral MOCR.

The MOCR has two distinct circuits, one that receives input from the same ear it controls (ipsilateral reflex) and one that receives input from the opposite ear (contralateral reflex). Animal data in cat and guinea pig has shown that more efferent fibers serve the ipsilateral reflex, so it was expected that human MOCR responses would be larger when activated ipsilaterally then activated contralaterally. Instead we found the responses, on average, to be equal near 1 kHz[1]. It is unclear why the MOCR needs contralateral reflex. Redundancy is one possibility, but the asymmetry found in at is not required for redundancy. The asymmetry found in cat and guinea pig is discussed within the context of a speculative 'head-shadow correction' role for the MOCR.

The sum of the ipsilaterally and contralaterally activated responses was found to be equal the bilaterally activated response on average at 1 kHz, and therefore no evidence of net binaural interaction was found.

C. Chapter 3: Time-course of the medial olivocochlear reflex

This chapter quantifies the time-course over which the effects of activating the MOCR build up in the cochlea.

In agreement with previous reports the reflex was found to act over two time scales (1) 100's of ms and (2) 10's of seconds. Our measurements quantify the faster time scale and show that the buildup is comprised of two time constants—fast ($\tau \sim 70$ ms) and medium ($\tau \sim 330$ ms)—and that the decay is best described by a damped sinusoid.

A second order model was able to describe both the buildup and decay by changing a single model parameter. A single second order process, located somewhere within the reflex loop, may govern the MOCR time-course (on the faster, 100's of ms, time scale).

The latency of the MOCR was ~25 ms and MOCR responses developed over 100's of ms which precludes the MOCR from providing any protection from loud impulse sounds such as gunshots.

[1] Measurements were made with SFOAEs near 1 kHz, whether ipsilateral/contralateral response differences exist at other frequencies remains to be seen.

D. Chapter 4: Efficacy of AM noise for activating the medial olivocochlear reflex

This chapter quantifies the efficacy of amplitude modulated (AM) wideband elicitors and unmodulated elicitors for activating the MOCR.

A previous study had demonstrated that contralaterally activated MOCR responses were larger when activated by amplitude modulated (AM) noise than when activated by unmodulated noise (Maison, Micheyl et al. 1999). We quantified contralateral MOCR responses to various rates of sine-wave and square-wave AM in an effort to replicate this finding. Three of 4 subjects did not show an increased response with AM of any rate, but one subject did show an enhanced response to 100 and 200 Hz AM. It was not determined, however, if the increases were due to time-dependent variations. Consequently, we do not know for certain whether AM modulation can increase responses for some subjects under some conditions. AM does not appear to generally increase MOCR responses.

'AC' and 'DC' components of MOCR responses were extracted for different modulation rates. DC responses were evident for those modulation rates (2 - 11 Hz) important in conveying speech information. This finding is discussed within the context of a 'speech perception in noise' role for the MOCR in hearing.

E. Chapter 5: Distribution of medial olivocochlear reflex strengths in normal-hearing humans.

This chapter quantifies the range and distribution of MOCR strengths in a normal-hearing population.

Prior studies in animals have indicated that the MOCR may help protect the ear from acoustic trauma (Rajan 1995). Furthermore, one study has demonstrated that that a stronger MOCR may provide more protection (Maison and Liberman 2000). Perhaps otoacoustic emission (OAE)-based tests could identify people susceptible to acoustic trauma. Only one study has so far presented normative data on MOCR strength (De Ceulaer, Yperman et al. 2001) and this study had some methodological problems (see Chapter 5 Discussion).

MOCR effects on single SFOAEs were found to be frequency-dependent, such that measurements made at nearby SFOAE frequencies (as close as 40 Hz) in the same subject did not return comparable results even after normalization designed to account for the differences in SFOAE amplitudes. This was unexpected. It was presumed that activating the MOCR with wideband noise would reduce the gain of

the cochlea uniformly across frequency, and it was presumed that this gain reduction was solely responsible for the resultant change in SFOAEs. The unexpected frequency-dependency of MOCR strength measures provides new insight into how the MOCR changes SFOAEs.

We found that averaging across frequencies (spanning 100 Hz) was able to reduce the frequency-dependence enough to generate consistent measures within a given subject. Using frequency-averaging, we were able to measure MOCR strength in 24/24 subjects and subsequently quantify the range and distribution of MOCR strengths near 1 kHz across a normal-hearing population.

The results are consistent with the idea that there may be 'tough' and 'tender' ears in humans. OAE-based tests (probably ones based on TEOAEs that naturally average across frequency) may prove useful for identifying people susceptible to acoustic trauma.

F. Chapter 6: Summary and future directions

This chapter provides summaries of the findings in chapters 2-5 as well as future directions associated with each chapter. It provides notes on experimental design gained from experience, the author's position on the role of the reflex in hearing, and reveals the author's choice for the next MOCR property to pursue as a 'new future direction.'

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Chapter 2: The Relative Strengths of the Ipsilaterally, Contralaterally and Bilaterally Activated Medial Olivocochlear Reflex in Humans

ABSTRACT

A comparison of ipsilaterally, contralaterally, and bilaterally-activated MOCR responses was made by measuring changes in SFOAE amplitudes induced with 60 dB SPL wideband noises. To avoid measuring two-tone suppression effects, MOCR responses were calculated from a 100 ms post-elicitor window during a time when two-tone suppression had vanished but MOCR effects continued to decay. Although efferent fiber counts and physiology in animals indicates that the ipsilateral MOCR is served by more efferent fibers than the contralateral MOCR (Guinan, Warr et al. 1984; Brown 1989) in animals, we did not find evidence that ipsilaterally-activated MOCR effects on OAEs in humans were larger than contralaterally-activated ones; instead, we found those effects to be, on average, equal (31 ears measured, using SFOAEs near 1 kHz). On average, the sum of the ipsilaterally and contralaterally-activated responses equaled the bilaterally-activated response, and consequently no prevailing binaural facilitation or inhibition was found at 1kHz using our 60 dB SPL wideband elicitor stimulus.

ABBREVIATIONS

B	B-MOCR response (short-hand)
BAS	bilateral acoustic stimulation
B-MOCR	bilateral MOCR
C	C-MOCR response (short-hand)
CAS	contralateral acoustic stimulation
C-MOCR	contralateral MOCR
DPOAE	distortion product otoacoustic emission
EC	ear canal
I	I-MOCR response (short-hand)
IAS	ipsilateral acoustic stimulation
ILD	interaural level difference
I-MOCR	ipsilateral MOCR
MOC	medial olivocochlear
MOCR	medial olivocochlear reflex
OAE	otoacoustic emissions
SFOAE	stimulus frequency otoacoustic emission
SNR	signal-to-noise ratio

I. INTRODUCTION

The medial olivocochlear reflex (MOCR) is one of several sound-activated feedback circuits that control the input to the mammalian hearing system (for a review see Guinan 1996). Activating medial olivocochlear (MOC) fibers reduces the amplitude of basilar membrane motion in response to sound by 10-20 dB at the characteristic frequency (Murugasu and Russell 1996; Dolan, Guo et al. 1997; Cooper and Guinan 2003).

The medial olivocochlear reflex in mammals is served by two distinct circuits (Figure 1) an ipsilateral (same ear circuit) and a contralateral (opposite ear circuit).

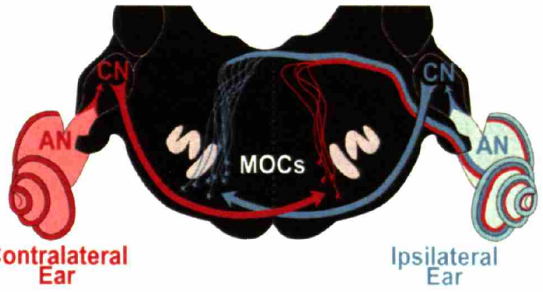

Figure 1. Schematic of the ipsilateral (blue) and contralateral (red) medial olivocochlear reflex circuits to the right ear. In cat and guinea pig it was found that there were generally more efferent fibers serving the ipsilateral reflex than the contralateral reflex reflected here by a plurality of ipsilateral efferents. AN = auditory nerve, CN = cochlear nucleus, MOCs = MOC neurons. Schematic courtesy Dr. Charles Liberman.

Anatomical data from animals suggests that the ipsilateral MOCR (I-MOCR) is served by more efferent fibers than the contralateral MOCR (C-MOCR), by a ratio ~2:1, although the exact ratio is frequency-dependent (Guinan, Warr et al. 1984; Brown 1989). In addition, physiological evidence from cat and guinea pig indicates that the ipsilaterally activated MOCR responses are larger than contralaterally activated ones (Robertson and Gummer 1985; Liberman and Brown 1986; Liberman, Puria et al. 1996). The above findings have led to the expectation that the I-MOCR response would be larger than the C-MOCR response in humans, although no anatomical data is available for humans and no direct link between efferent fiber counts and response magnitude has been established. This work tests whether ipsilaterally activated MOCR responses are greater than contralaterally activated ones in humans.

This study also tests whether there is evidence of binaural summation by investigating how the ipsilaterally and contralaterally activated responses combine to form the bilaterally activated response. Evidence of binaural summation might suggest a binaural processing role for the reflex.

We measured changes in stimulus frequency otoacoustic emissions (SFOAEs) induced by MOCR activation using ipsilateral, contralateral, or bilateral acoustic stimulation (IAS, CAS, BAS) with 60 dB SPL wideband noise in order to compare the effect of stimulus laterality on MOCR response magnitudes, and thereby deduce the relative strengths of the I-MOCR vs. C-MOCR vs. B-MOCR.

II. METHODS

We quantified response magnitudes of the I-MOCR, C-MOCR, and B-MOCR by measuring changes in stimulus frequency otoacoustic emissions (SFOAEs) in response to wideband noise presented ipsilaterally, contralaterally or bilaterally (3 'lateralities').

A. Overview

A "probe-tone" was played into the ear canal in order to generate an SFOAE from within the cochlea. This SFOAE combined with the probe-tone in the ear canal to produce a compound-tone[2], $\mathbf{C}(t)$, the ear canal sound pressure at the probe-tone frequency (Figure 2). If the acoustic probe-tone stimulus is invariant and middle ear transmission is invariant, i.e. if there is no middle-ear-muscle (MEM) contraction, changes in the compound-tone can be wholly attributed to changes in the SFOAE, i.e. $\Delta\mathbf{C}(t) = \Delta\mathbf{SFOAE}(t)$. Since activation of medial-olivocochlear (MOC) fibers reduces the sound-induced motion of the basilar membrane (BM) (Murugasu and Russell 1996; Dolan, Guo et al. 1997; Cooper and Guinan 2003) it is likely that MOCR inhibition of SFOAEs is caused by the reduction of BM motion[3].

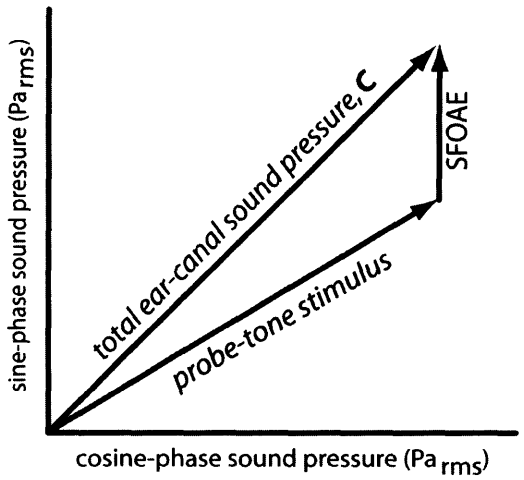

Figure 2. Vector diagram representing the summation in the ear-canal (EC) of two tonal components that differ in magnitude (length of arrows) and phase (direction of arrows). A tone stimulus (probe-tone) and the SFOAE it generates add to produce a compound-tone, C, that is measured as the EC sound pressure at the probe-tone frequency. If the probe-tone component is invariant, any change in the measured EC sound pressure reflects a change in the SFOAE magnitude and/or phase.

B. Subjects and screening

24 adult subjects (13 female, 11 male) were included in the study. A larger pool of 36 subjects was screened. 12 subjects were rejected because they did not meet a 20 dB signal to noise (SNR) criteria in either ear. All selected subjects had normal hearing in both ears (within 20dB re: ANSI pure tone threshold from 250 Hz to 4 kHz).

Probe-frequencies that produced large SFOAEs were chosen to be measured; some subjects were

[2] The compound-tone, $\mathbf{C}(t)$, is a complex quantity whose magnitude and/or phase can change over time, such that $\mathbf{C}(t) = |\mathbf{C}(t)| \cdot e^{i\angle\mathbf{C}(t)}$.

[3] Strong frequency dependant variations found in chapter 5 indicate that this may not be the only way in which MOCR activation can affect SFOAEs (see Chapter 5, Discussion)

measured at more than 1 probe-frequency. Each ear (both ears were measured simultaneously) produced an SFOAE at the probe-frequency that was 50 Hz or more from any spontaneous emission with an amplitude > -5 dB.

C. Acoustic stimuli

To produce an SFOAE, a continuous 40dB SPL probe-tone was presented *bilaterally* through two Etymotic ER10c earphones. Probe-frequencies used ranged from 500 – 7970 Hz, but a majority (20/30) were between 900 and 1100 Hz. The manuscript focuses on the 900 - 1100 Hz data. To elicit an MOCR response, a 2.5 s wideband (100 Hz - 10 kHz) ipsilateral, contralateral, or bilateral 60 dB SPL noise-burst (5 ms rise/fall) was presented every 5 s, alternating in polarity with each burst. Left and right ears were measured simultaneously, such that an ipsilateral noise presentation for the left ear constituted a contralateral presentation for the right[4]. For each subject, the 60 dB SPL noise-burst level did not elicit middle-ear-muscle contractions as shown by a group-delay test (test details in Chapter 3, Appendix A).

D. Analysis

Multiple (8-180) stimulus presentations were made and the resulting responses were averaged to form a measurement. The magnitude and phase of the average EC sound pressure at the probe-tone frequency, **C**(t), was extracted by heterodyning (Kim, Dorn et al. 2001; Guinan, Backus et al. 2003). Finally, the *change* in EC sound pressure over time, (due to the MOCR-mediated changes in the SFOAE over time) was calculated by vector subtraction to produce **ΔSFOAE**(t) (Figure 3). Specifically, the pre-elicitor average of **C**(t) (vector mean of **C**(t) in the time window: $-480 < t < -80$) was subtracted from each **C**(t) time point to compute **ΔSFOAE**(t).

[4] Each probe-tone frequency could produce two measurements in a given subject, one for the left ear and one for the right ear if both passed. a 20 dB SNR criteria (see Methods C2).

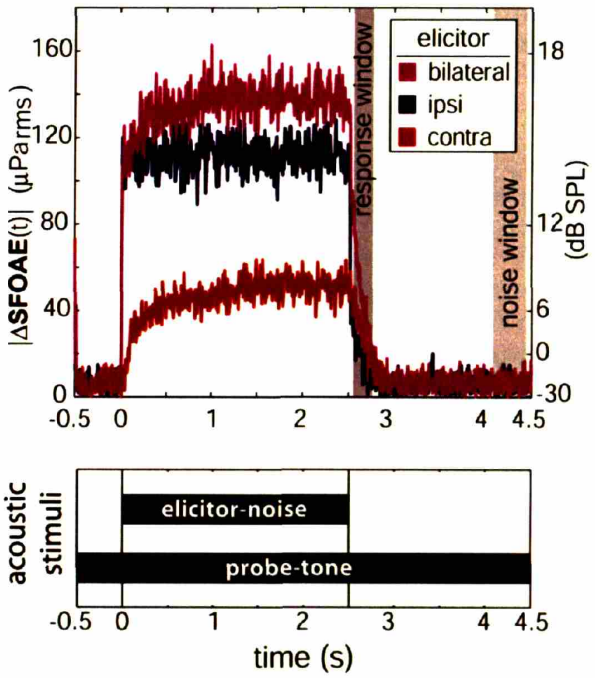

Figure 3. Changes induced in an SFOAEs by ipsilateral (blue), contralateral (red) and bilateral (purple) wideband elicitor-noise bursts (Top Panel). Bottom panel shows the acoustic stimulus presentation timing (elicitor-noise on between 0 s - 2.5 s). Since ipsilateral and bilateral elicitors evoke two-tone suppression (as seen by near instantaneous changes in the SFOAE), comparisons of MOCR effects across elicitor lateralities were made by averaging across a 100 ms post-elicitor response window (grey bar 2520 - 2620 ms) where two-tone suppression effects had vanished but where MOCR effects continued to decay. The average across a 300 ms 'noise window' 4180ms - 4480ms was used to quantify the noise floor level. (Subject F109R, probe-tone = 1100 Hz, 96 stimulus presentations averaged per laterality).

1. Calculating I-MOCR, C-MOCR, and B-MOCR response magnitudes

Ipsilateral and bilateral elicitor presentations evoke two-tone suppression, a local cochlear interaction that does not involve the MOCR but does change SFOAEs. Two-tone suppression effects develop and decay rapidly (within a few ms); MOCR effects are longer-lasting with time constants of 100's of ms (see Chapter 3). In order to compare I-MOCR and B-MOCR responses with C-MOCR responses, we exploited this difference and measured in a post-elicitor window after a 20 ms delay. The MOCR response for a particular laterality (*L*) was taken to be the magnitude of the complex average of the

ΔSFOAE(t) response in a 100 ms post-elicitor window (2520 < t <2620).

$$MOCR_{resp}(L) = \left| \frac{\sum_{t=2520ms}^{2620ms} \Delta\mathbf{SFOAE}(t, L)}{number\ of\ time\ samples} \right| \quad (1)$$

2. *Applying SNR criteria*

I-MOCR, C-MOCR and B-MOCR measurements forming a trial (a trial consisted of 3 measurements, one from each elicitor laterality, measured in a given ear at a given probe-tone frequency) were kept if the B-MOCR response magnitude exceeded its noise floor magnitude by a factor of 10 (20 dB). Otherwise the entire trial (all 3 measurements) was discarded. Noise floor magnitude was calculated as in Eq. 1 but over a 300 ms window (4180 - 4480 ms) using the bilateral presentation's response. This process insured large B-MOCR responses.

3. *Normalization by B-MOCR responses*

In order to compare I-MOCR vs. C-MOCR vs. B-MOCR responses all responses were normalized by the B-MOCR response from the same trial. All responses are presented in fraction of B-MOCR response (B-MOCR responses are 1 by definition).

III. RESULTS

Individual data from all trials and their average are shown in Figure 4. Different frequency ranges were measured but no obvious trends with frequency were observed[5]. For a given trial, either the I-MOCR response (I) or the C-MOCR response (C) was larger, and no trend was observed (data were scattered equally above and below line I = C). Also, I + C could either be larger or smaller than measured B-MOCR responses (B). Methodological issues prevent us from determining whether individual points departed significantly from either (1) I=C, or (2) I+C = B.

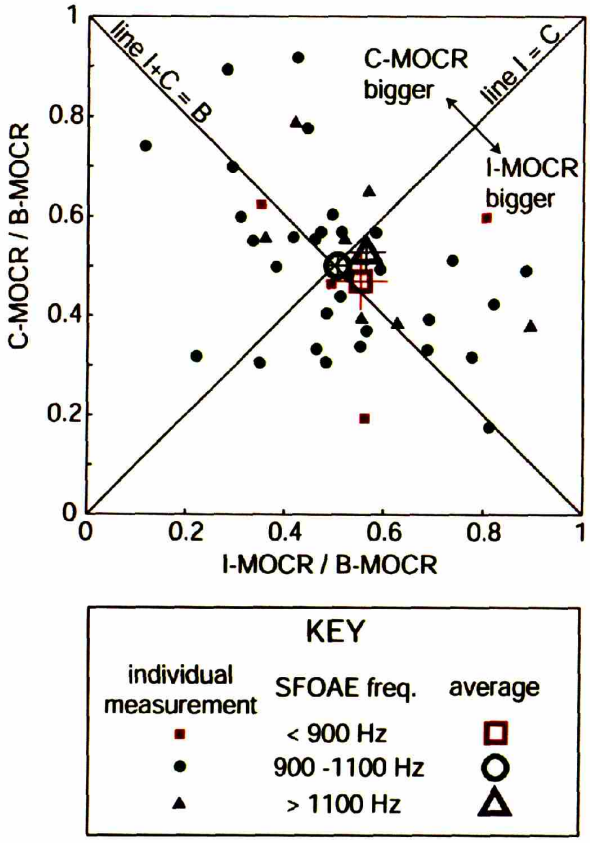

Figure 4. Comparison of ipsilateral (x-axis) vs. contralateral (y-axis) MOCR responses. Small symbols are individual measurements from 24 subjects at various SFOAE frequencies (different shapes/colors). Responses were evoked with 60 dB SPL wideband noise and were normalized by an associated bilateral response. On average, I-MOCR and C-MOCR responses: (a) were equal (large symbols near line I = C), and (b) ~summed to the bilateral response (large symbols near line I + C = B), thus no prevailing binaural facilitation or inhibition was evident (24 subjects measured, various SFOAE frequencies).

There were enough measurements (31) using SFOAEs within 10% of 1 kHz (900 – 1100 Hz) to make good laterality comparisons near 1 kHz. On average the I-MOCR and C-MOCR both produced effects on SFOAEs near 1 kHz that were 50% of the B-MOCR response (50.6%+/-2.7%, 50.0%+/-2.6% respectively) (Figure 5). The fact that I+C = B held for the average (I+C = 100.6%+/-5.3%, compare with B = 100%) indicated that there was no *prevailing* binaural interaction (facilitation or inhibition) to our 60 dB SPL wideband noise stimulus (at 1 kHz).

[5] There were not enough measurements using the '< 900 Hz' or '> 1100 Hz' SFOAE to make trends obvious, or to generate trustworthy averages for these ranges.

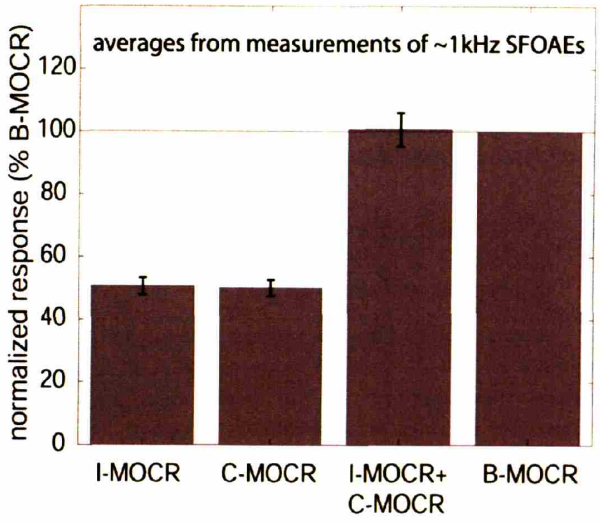

Figure 5. Comparison of average MOCR responses across 31 ears (16R 15L from 19 subjects) induced by either ipsilaterally, contralaterally, or bilaterally presented 60 dB SPL wideband noise shows that I-MOCR and C-MOCR responses are, on average, equally capable of altering SFOAEs near 1 kHz (SFOAEs between 900 - 1100 Hz were averaged). Furthermore the sum of (average) I-MOCR + C-MOCR responses predicted the B-MOCR response very accurately indicating that there was no prevailing binaural interaction for wideband noise activators.

IV. DISCUSSION

A. Concerns about the measurement method

Our methods used in this study have the following shortcomings:

(1) The short duration (100 ms) post-elicitor 'window' over which the response is averaged contains only 20 samples and is susceptible to random noise.

(2) Averaging across a post-elicitor window generates a single response value but that value is calculated over a region where the response is decaying. Any comparison of those values across presentation literalities presumes similar decay rates (and offset delays) for all lateralities. The response value does not quantify a steady-state response.

(3) Error due to 'baseline-drift' (see Chapter 5, Methods) was not quantified or removed; therefore individual measurement points (Figure 4) may contain drift and may not accurately reflect the individual's response (i.e. there is reason to believe that individual points will not be repeatable).

Individual data points are not accurate enough to be trustworthy on their own; however, shortcomings (1) and (3) are mitigated when individual points are averaged. Shortcoming (2) is not mitigated for the average if there is a *systematic* difference in the decay rates for different presentation literalities. Chapter 3, Results C suggests that no such systematic differences in the decay time-course exist. Therefore, we can reasonably trust the aggregate results (in Figures 4, 5).

B. Comparison of the relative strengths of ipsilaterally vs. contralaterally-elicited MOCR responses with expectations based on anatomical data from animals

Figure 6 shows that efferent fibers serving the ipsilateral MOCR are more numerous than those serving the contralateral MOCR over a wide frequency range in cat. The difference appears grow with frequency (Guinan, Warr et al. 1984). This finding is consistent with DPOAE-based MOCR measures in cat that showed ipsilateral MOCR effects were roughly twice contralateral MOCR effects (Liberman, Puria et al. 1996). It is also consistent with characterizations of single MOC fibers in guinea pig that showed a majority (57%) responded to ipsilateral sound less responses to contralateral sound (28%) and (15%) responded to either laterality (Brown 1989).

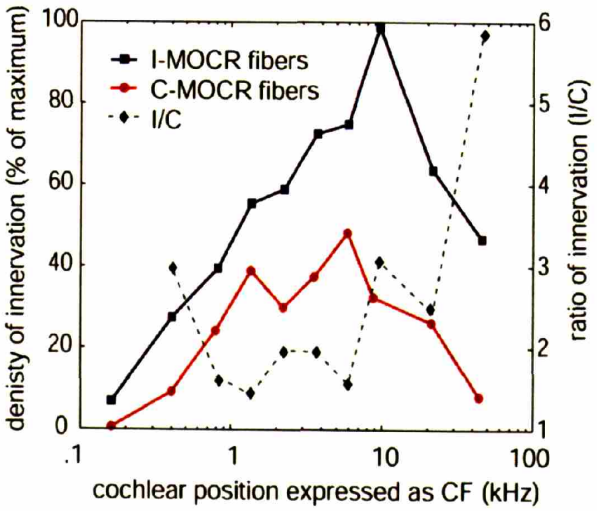

Figure 6. Efferent fiber densities serving the ipsilateral (blue), and contralareral (red) MOCR across frequency (Guinan, Warr et al. 1964) show that there are more efferent fibers serving the ipsilateral reflex, and the

difference (dash line) is frequency-dependent. Note that the fiber counts are actually from crossed (blue) and uncrossed (red) efferent pathways, but animal work suggests that the vast majority of crossed efferent fibers serve the ipsilateral reflex and the vast majority of uncrossed efferent fibers serve the contralateral reflex. Figure adapted from one courtesy of Dr. J. Guinan.

These anatomical and physiological findings in animals led to the expectation that ipsilateral MOCR responses would be larger than contralateral ones in humans; but our results (Figures 4, 5) do not show the expected difference. It is possible that human MOCR anatomy and physiology is different from cat and guinea pig, or that more efferent fibers does not necessarily translate into increased MOCR responses as measured via 1 kHz SFOAEs.

B. Why do we have two different MOCR pathways?

"Why do we have two different MOCR reflex circuits?" One hypothesis is that multiple circuits provide redundancy. Redundancy, however, does not account for the I-MOCR/C-MOCR asymmetry found in animals. A second speculative hypothesis is that the two circuits provide a 'load-balancing' mechanism whereby the gain of each ear is controlled in a frequency-dependent way to maximize the combined information from both ears[6]. In this capacity, asymmetry might be expected. For example, frequency-specific differences (such as efferent fiber density) could be related to the 'head shadow' effect—whereby high frequencies are blocked by the head[7]. 'Correcting' for head shadow, however, would deteriorate spatial cues, such as interaural level difference (ILD), within the auditory nerve.

C. Evidence for binaural interactions

Binaural responses were always larger than ipsilateral or contralateral responses, in agreement with previous reports (Berlin, Hood et al. 1995), but in addition we found that the sum of the monaural responses was equal, on average, to the binaural response. Consequently, there was no evidence that a prevailing binaural inhibition or facilitation is triggered by uncorrelated noise elicitors (Figure 5). Individual results in Chapter 3 Results C did show that for one ear/SFOAE combination I+C = B did not hold[8]. These are new findings.

There has been some recent evidence to suggest that correlated noise elicitors may produce an interaction (Kemp, Hsueh et al. 2005).

D. A new method for measuring the relative strengths of ipsilaterally contralaterally and bilaterally activated MOCR

A new method for measuring and quantifying the relative I-MOCR, C-MOCR and B-MOCR responses allows measurement of the steady-state responses. This new method is reported in Chapter 3. It uses notched-noise (with a notch bandwidth centered at the probe-tone frequency and chosen to be wide enough to remove two-tone suppression) rather than a post-elicitor averaging window to remove two-tone suppression effects. The new method has the advantage that steady-state responses can be measured and compared rather than responses that are decaying over time.

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[6] In other words, the MOCR would constitute a pre-processor for binaural processing.

[7] Significant head-shadowing starts at ~2 kHz in cat and ~1 kHz in humans.

[8] The data in Chapter 3, Results C was gathered using interleaved trials, so the departure from I+C=B for subject F109R is not likely to be due to time-dependent variations.

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Chapter 3: Time-course of the Human Medial Olivocochlear Efferent Reflex

ABSTRACT

The time-course of the human medial olivocochlear reflex (MOCR) was measured using stimulus frequency otoacoustic emissions (SFOAEs) in nine ears from eight subjects. MOCR effects were elicited by contralateral ipsilateral or bilateral wideband acoustic stimulation. As a first approximation, MOCR effects built up like a saturating exponential with a time constant of 277 ± 62 ms, and decayed exponentially (following noise burst cessation) with a time constant of 159 ± 54 ms (9 ears). However, when more resolution was possible (4/9 ears) the MOCR onset time constant could be separated into underlying 'fast', τ = ~70 ms, 'medium', τ = ~330 ms, and slow, τ = ~25 s time constant components. The high resolution ears also showed an overshoot in the decay that could be characterized as a damped sinusoid. Both the buildup and the decay could be modeled as a second order differential equation. The difference between the buildup and the decay could be accounted for by decreasing the 'damping coefficient' by a factor of 2. Both the reflex onset and offset delays were ~25 ms. The time-course was not systematically affected by elicitor level, nor did the time-courses of ipsilaterally, contralaterally, and bilaterally activated MOCR responses differ significantly. Given the speed of the MOCR, it is best suited to operate on acoustic changes that persist for 100's of milliseconds.

ABBREVIATIONS

BM	basilar membrane
C(t)	time varying complex compound-tone (measured)
CAS	contralateral acoustic stimulation
CF	characteristic frequency
CM	cochlear microphonic
DPOAE	distortion-product otoacoustic emission
EC	ear-canal
EP	endolymphatic potential
MEM	middle ear muscle
MEMR	middle ear muscle reflex
MOC	medial olivocochlear
MOCR	medial olivocochlear reflex
OCB	olivocochlear bundle
OHC	outer hair cell
P	significance probability (P < 0.05 is considered statistically significant)
PSTH	post stimulus time histogram
R	correlation coefficient
SNR	signal to noise ratio
SFOAE	stimulus-frequency otoacoustic emission
ΔSFOAE(t)	time varying change in complex stimulus frequency emission (calculated)
SOAE	spontaneous otoacoustic emission
TEOAE	transiently-evoked otoacoustic emission
VS	vector strength

I. INTRODUCTION

The medial olivocochlear reflex (MOCR) is one of several sound-activated feedback circuits that control the input to the mammalian hearing system (for a review see (Guinan 1996). Activating medial olivocochlear (MOC) fibers reduces the amplitude of basilar membrane motion in response to sound by 10-20 dB at the characteristic frequency (CF) (Murugasu and Russell 1996; Dolan, Guo et al. 1997; Cooper and Guinan 2003). Despite general knowledge about how the MOCR changes cochlear and neural responses to sound, a fundamental question remains, "What use is the MOCR?" Understanding how fast the MOCR produces its effects can suggest auditory processing that is affected by the MOCR. And quantification of the time constants that describe the MOCR time-course can help determine which cellular processes are involved by focusing attention on those processes with similar time constants.

The discovery that otoacoustic emissions (OAEs) (Kemp 1978) are modulated by MOC activation (Mountain 1980; Siegel and Kim 1982) has led to the investigation of the MOCR in humans via its effects on OAEs. Several investigations have used OAE-based measurements to pursue the MOCR time-course (Kim, Dorn et al. 2001; Maison, Durrant et al. 2001). However, interpreting the very different results

from these transient and distortion product otoacoustic emission (TEOAE and DPOAE) studies is complicated by intra-cochlear interactions[9] such as two-tone suppression and by efferent activation by the test stimuli.

One way to avoid these complications is to use stimulus-frequency otoacoustic emissions (SFOAEs). SFOAE-based methods require only one low-level probe-tone thereby avoiding multiple frequency interactions, providing the most frequency-specific measure, and reducing the likelihood that the probe itself will elicit efferent activity (Guinan, Backus et al. 2003).

We used an SFOAE-based method to quantitatively answer five questions: (1) How rapidly does the MOCR produce its effects in the cochlea? (2) How rapidly do those effects decay? (3) Is there a relationship between the buildup and decay? (4) Is there any difference in the time-course when more intense elicitor stimuli are used? (5) Is there any difference in the time-course between the ipsilaterally, contralaterally, and bilaterally elicited reflexes?

II. METHODS

A. Overview

A "probe-tone" was played into the ear canal in order to generate an SFOAE from within the cochlea. This SFOAE combined with the probe-tone in the ear canal to produce a compound-tone[10], **C**(t), the ear canal sound pressure at the probe-tone frequency, (see Figure 7). If the acoustic probe-tone stimulus is invariant, e.g. if there is no middle-ear-muscle (MEM) contraction (see Appendix A), changes in the compound-tone can be wholly attributed to changes in the SFOAE. Since activation of medial-olivocochlear (MOC) fibers reduces the sound-induced motion of the basilar membrane (BM) (Murugasu and Russell 1996; Dolan, Guo et al. 1997; Cooper and Guinan 2003) it is likely that a portion of the MOCR inhibition of SFOAEs is caused by the reduction of BM motion (for a discussion of different mechanisms by which MOCR activation may change SFOAEs see Chapter 5, Discussion A).

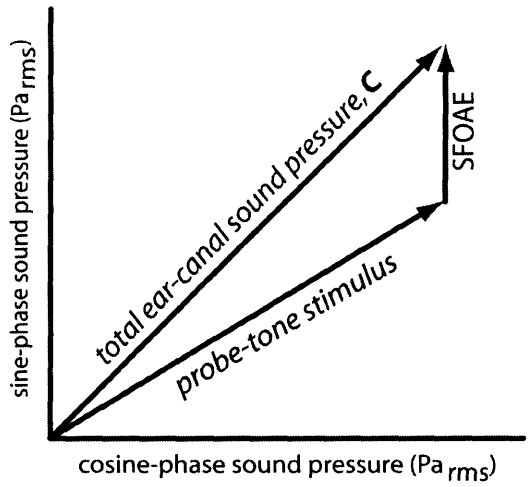


Figure 7. Vector diagram representing the summation in the ear-canal (EC) of two tonal components that differ in magnitude (length of arrows) and phase (direction of arrows). A tone stimulus (probe-tone) and the SFOAE it generates add to produce a compound-tone, C, that is measured as the EC sound pressure at the probe-tone frequency. If the probe-tone component is invariant, any change in the measured EC sound pressure reflects a change in the SFOAE magnitude and/or phase.

We used a continuous (40 dB SPL) bilateral probe-tone near (within 12% of) 1 kHz to produce an SFOAE and to create thereby a compound-tone. A heterodyne technique (Kim, Dorn et al. 2001; Guinan, Backus et al. 2003) was used to extract the magnitude and phase of the compound-tone across time, **C**(t), while a second acoustic stimulus, the elicitor (see below), was introduced to activate the MOCR and thereby alter the SFOAE and the measured **C**(t). Changes in the compound tone, $\Delta\mathbf{C}(t)$, were calculated by vector subtracting the average pre-elicitor **C**(t)[11] from each time point in **C**(t). The result, $\Delta\mathbf{C}(t)$, quantifies changes from the no-elicitor condition (for details see (Guinan, Backus et al. 2003).

We strove to keep the probe-tone stimulus invariant by using elicitor levels below middle-ear-muscle reflex (MEMR) thresholds and by asking subjects to be as still as possible during measurements. To test whether our elicitor levels ($\leq$ 60 dB SPL) were below MEMR thresholds, we performed "phase-slope MEMR tests" in which we calculated the phase-slope of $\Delta\mathbf{C}$'s produced by a 60 dB SPL wide-band noise

[9] Each of these methods requires that multiple frequencies be presented into the measurement ear simultaneously.

[10] The compound-tone, **C**(t), is a complex quantity whose magnitude and/or phase can change over time, such that $\mathbf{C}(t) = |\mathbf{C}(t)| \cdot e^{i\angle\mathbf{C}(t)}$.

[11] The pre-elicitor average of **C**(t) was the average in a time window from -450 to -50 ms prior to elicitor onset. Note that time is always reported relative to elicitor onset.

elicitor (Appendix A). No ears had measurable MEMR effects at elicitor levels of 60 dB SPL.

Because SFOAE amplitudes vary widely across frequencies and ears, our measurements of MOCR effects are reported in units relative to an estimate of the SFOAE amplitude. In other words, our MOCR measurements are *normalized* and are reported as 'Δ**SFOAE**(t)' with units of %|**SFOAE**| (for detail see Appendix B). Without normalization one cannot compare the magnitude of MOCR effects across ears and/or frequencies as the widely varying SFOAE amplitudes will be reflected in the responses.

B. MOCR elicitor stimuli

Two and a half second 60 dB SPL wide-band (100 Hz – 10 kHz) noise bursts repeated every 5 seconds were used to activate the MOCR. Because wide-band noise induces two-tone suppression effects when presented into the measurement ear, we only used contralateral wide-band noise elicitors. When ipsilateral and bilateral activation of the MOCR was required (for looking at the ipsilateral and bilateral MOCR time-course) we used notched-noise elicitors. For these, a 2.1 octave spectral notch centered at the probe-tone frequency was used to remove energy from the wide-band noise elicitor at frequencies that produced measurable two-tone suppression effects (details in Appendix E).

C. Subjects and screening

Of 28 subjects screened for the study, nine young adult subjects, 19 to 30 years of age, were chosen to participate (8 female, 1 male). Participation was contingent on passing four tests: 1. A two-interval forced choice audiogram using 1/3 octave band noise bursts centered at 250Hz, 500Hz, 1kHz, 2kHz, and 4kHz was used to insure subjects had normal hearing in both ears (within 20 dB re: ANSI pure tone thresholds). 2. Measurements of spontaneous emissions in quiet were used to insure that the probe-tone was at least 50 Hz from any spontaneous emission[12] greater than -5 dB SPL. 3. A MEMR phase-slope test (Appendix A) was used to insure that MOCR effects dominated the measured changes in the compound-tone. 4. A signal to noise ratio (SNR) test[13] was applied to the results and was used to select those subjects for whom turning on the elicitor noise produced a clear, strong and consistent $\Delta\mathbf{C}(t)$ signal.

D. Choosing a probe-tone frequency

Selecting ear/probe-tone-frequency combinations that produced large SFOAEs and thereby high SNR measurements was important for looking at details of the MOCR time-course. For this reason, each subject was initially measured at 11 or 12 probe-frequencies (20 Hz steps from 900-1100 HZ or from 900 – 1200 Hz); and then the ear/probe-tone-frequency combination that yielded the largest $\Delta\mathbf{C}(t)$ response was selected for further measurements. Initial measurements used 40 dB SPL continuous bilateral probe-tones and 60 dB SPL bilateral wideband noise elicitors (2500 ms in duration). The response was taken to be the average $|\Delta\mathbf{C}(t)|$ in a post elicitor window, 50 - 150 ms after elicitor cessation.

E. Measurement procedure

Subjects were comfortably seated in a sound-dampening chamber during 30 minute measuring sessions that were interleaved with 15 minute breaks. Some subjects took several hours to measure and were measured over multiple days.

In every session, two earphones (Etymotic Research ER10c) each containing two sound sources and one microphone, were fitted in the subject's ear canals, one in each ear. To eliminate potential distortion, one source from each ER10c was allocated exclusively to the continuous probe-tone stimulus while the second source was used for the elicitor (or suppressor) stimulus. Calibrations were done at the

[12] Because spontaneous emissions can be entrained (Van Dijk and Wit 1988), they may shift toward and interact with the probe-tone stimulus confounding SFOAE-based measures (Burns, Strickland et al. 1984). To resolve this issue, once a potential measurable probe-tone frequency was identified, two buffers (2621 ms each) were acquired from the microphones in quiet and their spectra were averaged. If any spontaneous emission > -5 dB SPL was detected within 50 Hz of the prospective probe-tone frequency, then a new probe frequency was chosen.

[13] The criterion for acceptable SNR was 95% phase coherence, defined by a vector strength (VS) > 0.95 in a time window during the elicitor (i.e. 1950 ms to 2450 ms, see Table 1). Phase coherence was used because coherent phase is a strong indicator of signal presence. Vector strength was calculated by adding vectors of unity magnitude but with phase values taken from the data points in the time window (Goldberg and Brown 1969) (n in the equation below represents indexes to these ~500 consecutive samples). The resultant sum vector was then divided by the total number of vectors included in the sum, and its length had to be > 0.95:

$$VS = \frac{1}{N}\sum_{n=1}^{N} e^{i\angle\mathbf{C}(n)} > 0.95$$

beginning, during, and at the end of every measuring session to insure proper sound pressure levels for all stimuli[14]. Stimuli were created digitally (sampling rate of 20 kHz) and stimulus levels were set by attenuators (0.1 dB accuracy). A raised cosine ramp (5 ms rise and fall) reduced spectral splatter for the pulsed stimuli. Microphone signals were digitized using the same 20 kHz sample timer used for stimulus generation.

Elicitor and suppressor stimuli were adjusted to suit each measurement type (see Table 1). For instance, because MOCR effects develop slowly compared to two-tone suppression effects, the stimulus durations for noise elicitors used in MOCR measurements (and also in the MEMR test) were 2500 ms while the stimulus durations for suppressor-tone stimuli used for **SFOAE** estimation were either 500 ms or 200 ms. MOCR elicitors were 60 dB SPL wideband (100 Hz – 10 kHz) noise except during a) level-dependence experiments where 40, 45, 50, 55, and 60 dB SPL elicitors were used and b) laterality-dependence experiments where the elicitor was a wideband noise with a 2.1 octave spectral notch centered at the probe-tone frequency. Suppressor-tone stimuli were tones at 60 dB SPL placed -110 Hz re: the probe-tone frequency (except during suppression bandwidth measurements for which the suppressor-tone frequency was varied.)

Every measurement consisted of an average of an even number of presentations. Elicitor (or suppressor) polarities were alternated on successive presentations to cancel their acoustic contributions to the averaged EC sound pressure. This manipulation did not appear to have any effect on the emission.

[14] Changes in the calibrations usually indicated the earphone had moved. When a calibration failed, i.e. the requested sound level could not be produced, refitting the earphone assembly cured the problem.

Table 1 tabulates all stimuli used in this paper.

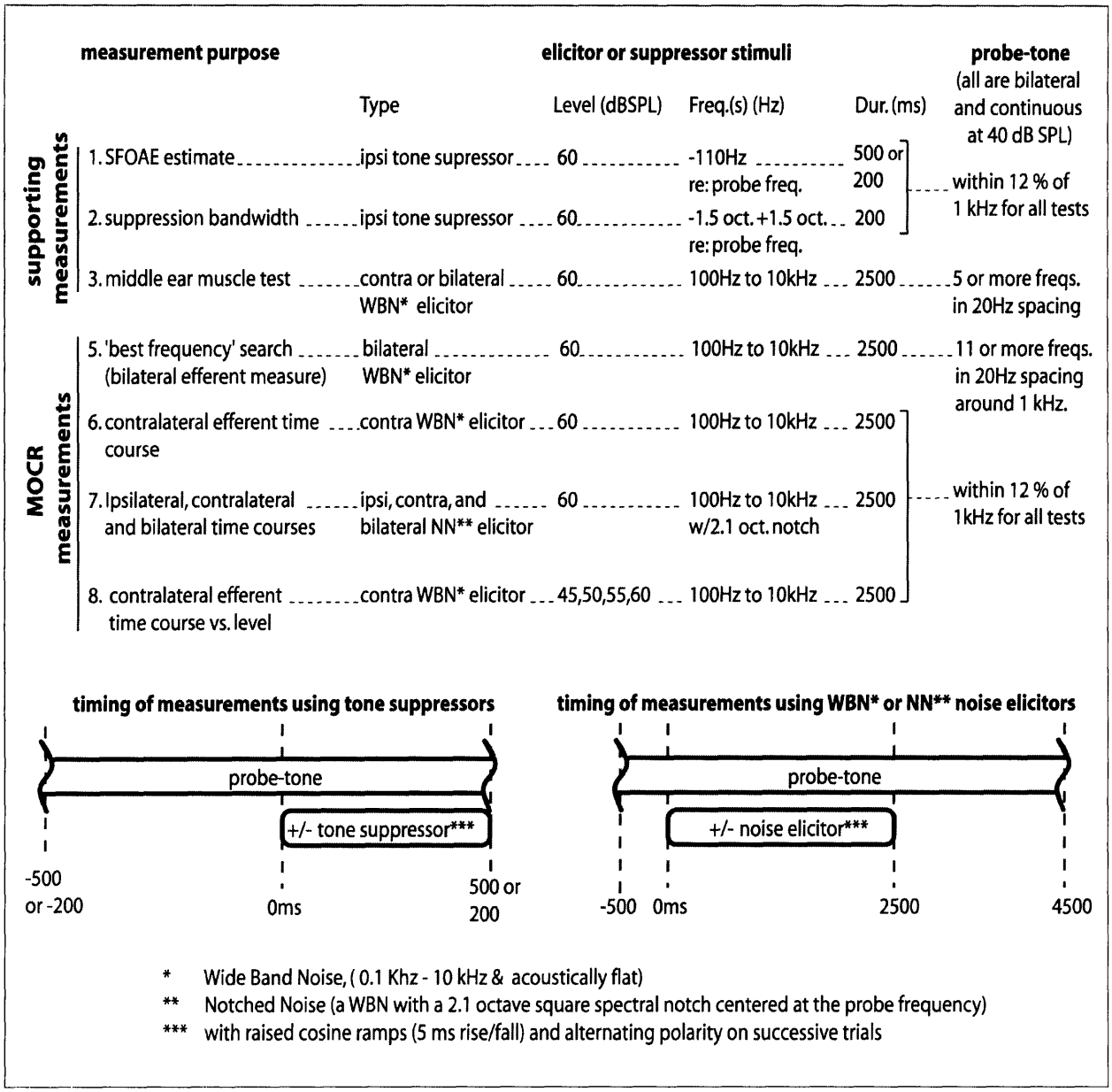


Table 1. Stimulus types (top panel) and stimulus presentation timings (bottom panel) for all measurements. To form a measurement, an even number (44 to 816 depending on SNR and subject availability) of presentations were made and the acoustic responses were averaged.

F. Mathematical characterizations of the responses

Each MOCR response waveform, Δ**SFOAE**(t), was characterized mathematically to quantify its time-course. We sought to characterize each waveform's rising curvature, decaying curvature, onset delay, and offset delay (for equations and details see Appendix C).

1. 'Single complex exponential' characterization

Our first characterization used a single complex saturating exponential term to represent the rising

curvature, a single complex decaying exponential term to represent the decaying curvature, and included onset and offset delay parameters (the amount of time between elicitor onset or offset and a change in the response). This 'single-complex-exponential' characterization provided reasonable approximations to the curvatures and was useful for the purpose of assigning an *overall onset time constant* and an *overall decay time constant* to the rising and decaying portions of the waveforms respectively.

2. *'Sum of complex exponentials' characterization*

Although the 'single complex exponential' characterizations captured the basic curvatures of the waveforms, subjects with high SNR measurements produced curvatures that differed visibly from their 'single-exponential' characterization (e.g. a bounce in the decay of subject 61R in Figure 8). To describe these waveforms better, a more complicated mathematical characterization, using a sum of complex exponential terms, was made (for details see Appendix C). These 'sum-of-exponentials' characterizations better approximate the waveforms, and they were used to quantify the onset and offset delays, and, when the SNR was large enough, to extract and quantify multiple time constants.

III. RESULTS

A. THE CONTRALATERAL MOCR TIME-COURSE

Both the amplitude and phase of SFOAEs were affected by MOCR activation; however, since most important aspects of the time-course can by shown by the amplitude alone, this paper focuses on amplitude changes. The MOCR manifested its effects on the amplitude of SFOAEs over 100's of milliseconds; and produced onset rises and offset decays that looked roughly like saturating and decaying exponentials (Figure 8).

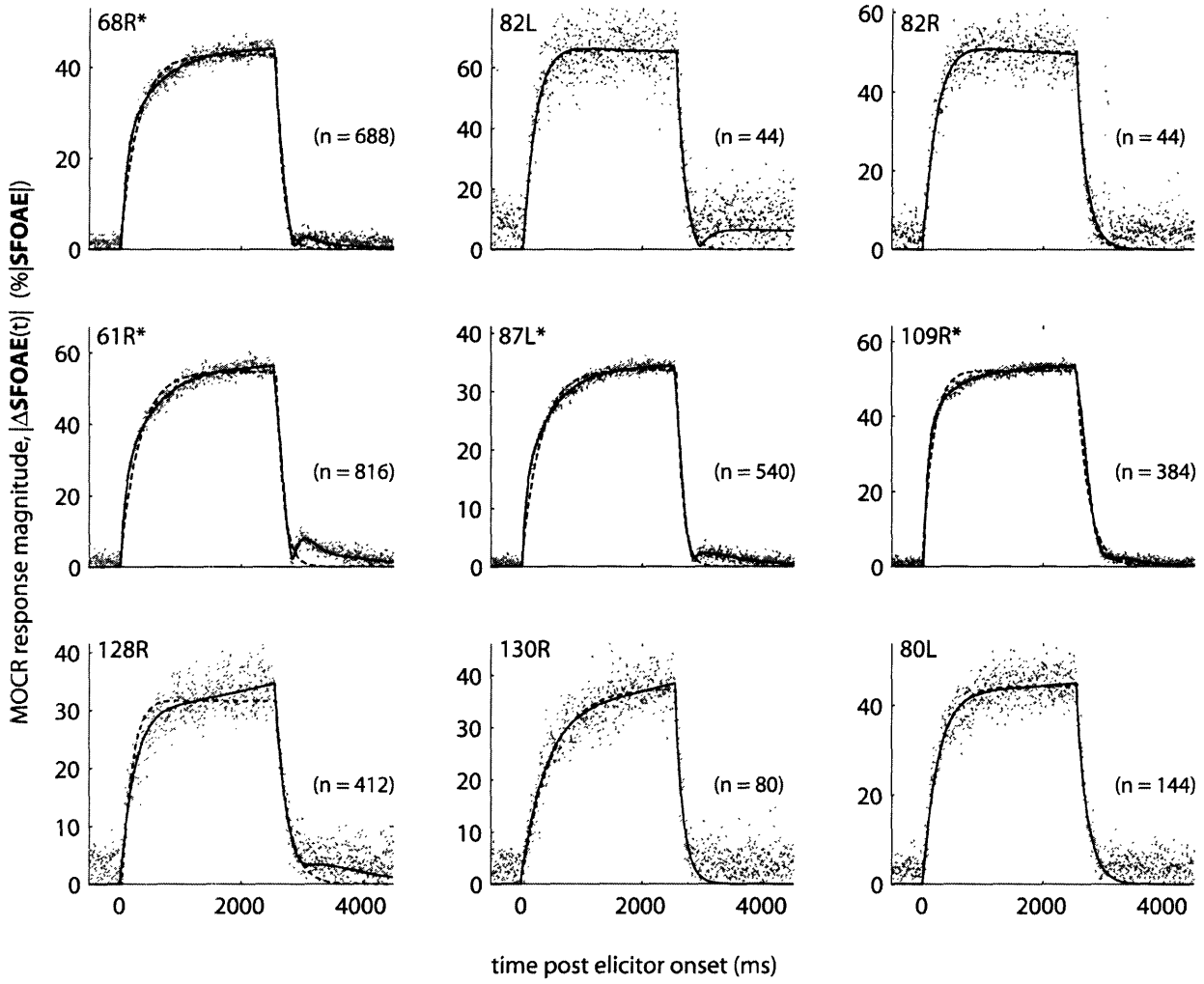


Figure 8. MOCR time-courses for 9 ears (no special order). Responses were evoked by contralateral wideband noise (60 dB SPL). Repetition interval was 5 sec and 'n' is the number of responses that were averaged for each measurement. Points are data samples (5 ms resolution), dashed curves are 'single exponential' characterizations, and solid curves are 'sum of exponentials' characterizations of the data. The 4 subjects with *'s are those with the 4 highest SNRs.

1. MOCR overall onset and decay time constants

We assigned a single overall time constant to the rising and falling portion of each MOCR response (associated curves have dashed lines in Figure 8). Estimates of overall onset and decay time constants varied from ear to ear, spanning 178 - 400 ms for the onset and 104 - 259 ms for the decay. For 7 of 9 ears the decay was more rapid than its buildup (Figure 9). Only ear 109R showed the opposite trend significantly with an overall onset time constant of 178 ± 3.2 ms, 35ms faster than its overall decay time constant (213 ± 3.0 ms). There was an apparent inverse relationship between the speed of the MOCR's onset and decay (R = -0.48, P = 0.15).

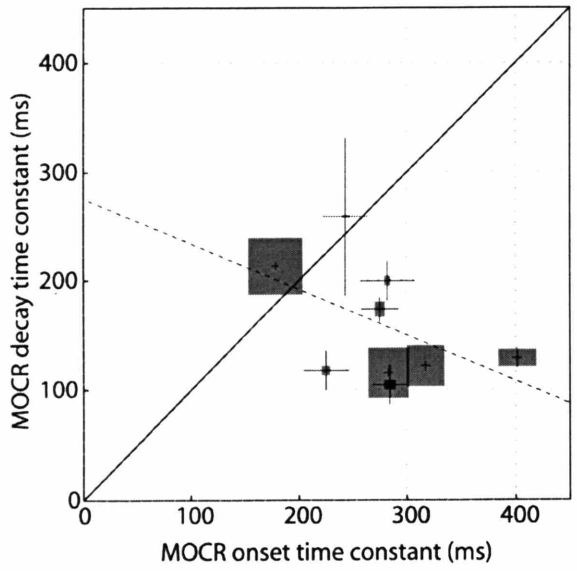


Figure 9. MOCR overall onset vs. decay time constants for 9 ears show that MOCR effects generally buildup more slowly than they decay. There was an apparent inverse relationship between the speed of the buildup of MOCR effects and the speed of the decay of those effects (dashed line, R = -0.48, P=0.15). Error bars = 1 SD (for details see Appendix C3). To emphasize more accurate data points, i.e. those with small error bars, rectangles, whose areas represent relative accuracy, are centered on each data point (bigger area means more accurate).

2. *MOCR effects can decay with an overshoot*

While the rising phase of each response was monotonic and appeared to approach a steady state like a saturating exponential, the decaying portion in 6 of 9 ears exhibited a 'bounce' that defied exponential decay (see Figure 8). This bounce led us to pursue a more complicated 'sum of complex exponentials' characterization.

With a 3 term 'sum of complex exponentials' we were able to mathematically characterize the bounce. The decay curvatures of the 4 highest SNR subjects (61R. 87L. 68R. and 109R) were well approximated by the combination of an under-damped sinusoid and a 'long' decay time constant (see Appendix D) indicating that the observed bounces were in fact an overshoot. In other words, as the SFOAE re-equilibrates to its pre-MOCR activation level (upon elicitor cessation), it can overshoot that level before returning to it. Phase data (not shown) corroborates the overshoot.

3. *MOCR overall onset time constant is primarily a combination of 'fast' and 'medium' underlying time constants*

The 'sum of exponentials' characterization was also a better approximation of the MOCR's onset response, as evidenced by higher goodness-of-fit values, R^2. For the four highest SNR ears, the MOCR onset time constants (Figure 10, Table 2) were found to be composed of a mixture of 'fast', ~70 ms, 'medium', ~330 ms, and 'slow', ~25 s, time constants with the bulk (88-93%) of the time-courses displayed in Figure 8 coming from the 'fast' and 'medium' time constants (low SNR subjects could not yield more than 2 distinct onset time constants. When they did produce 3, the 'fast' and 'medium' time constants had overlapping error bars).

As shown in Figure 10, ears 61R and 109R differed widely in their overall onset time constants (317 ± 4.59 ms vs. 179 ± 3.2 ms), yet their 'fast' and 'medium' underlying onset time constants were similar (69 ± 31 ms vs. 65 ± 10 ms and 331 ± 106 ms vs. 294 ± 68 ms). For these subjects, it was a different mix of 'fast' and 'medium' underlying onset time constants that produced their different overall onset time constants. Subjects 61R, 68R, 87L, and 109R all had sufficient SNR to allow the extraction of 'fast', 'medium', and 'slow' onset time constants. All generated consistent 'slow' onset time constants (10's of seconds) and quantitatively similar 'fast' (~70 ms) and 'medium' (~330 ms) onset time constants (Figure 10).

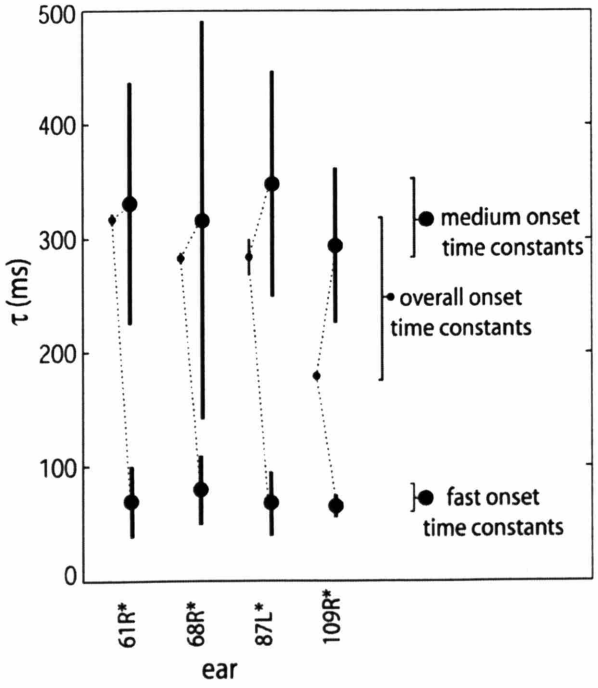


Figure 10. Onset time constants of MOCR responses from the 4 high SNR subjects show how underlying 'fast' and 'medium' time constants combine to generate an overall time constant. MOCR overall onset time constants (small circles) were estimated from 'single complex exponential' characterizations of individual MOCR waveforms and varied significantly across subjects. Underlying 'fast' and 'medium' onset time constants (large circles) were estimated from a 'sum of complex exponentials' characterizations and indicated that each subject had a fast (~70ms) and medium (~330 ms) onset time constant and that these did not vary significantly across subjects. The relative amounts of these subjects' 'fast' vs. their 'medium' time constants produced the different overall time constants. Error bars indicate standard deviations.

Table 2 tabulates the time constants.

ear	fast onset time constant (ms)	medium onset time constant (ms)	slow onset time constant (s)	overall onset time constant (ms)	overall decay time constant (ms)	long decay time constant (ms)
61R*	69±31 (27±12%)	331±106 (61±11%)	~18 (12±4%)	317±5	122±5	918±97 (14±1%)
68R*	79±30 (43±16%)	316±175 (49±15%)	~23 (8±3%)	283±5	115±4	594±254 (29±14%)
87L*	67±28 (31±11%)	348±99 (61±9%)	~27 (8±3%)	284±16	104±18	615±150 (21±6%)
109R*	65±10 (58±7%)	294±68 (35±7%)	~39 (7±2%)	179±4	213±3	449±52 (27±6%)
	undifferentiable					
80L	235±24 (88±5%)		~37 (12±5%)	275±18	173±12	unmeasureable
82L	197±23 (97±3%)		unmeasureable	225±21	118±12	unmeasureable
82R	229±14 (98±1%)		unmeasureable	243±21	259±73	unmeasureable
128R	223±18 (84±2%)		~14 (16±2%)	282±26	199±18	unmeasureable
130R	404±50 (79±5%)		~11 (21±5%)	401±5	129±10	unmeasureable

Table 2. Onset and decay time constants from MOCR responses to contralateral noise for 9 ears. Subjects 61R, 68R, 87L, and 109R had sufficiently large SNR to extract multiple time constants for the rising curvature. For these subjects, the MOCR onset (overall time constant) appears to be composed primarily of 'fast' ~70 ms and 'medium' ~330 ms time constants (percentages are the relative amounts of contribution to the time-courses). Low SNR subjects (80L, 82L, 82R, 128R, and 130R) could not distinguish 'fast' time constants from 'medium' ones. MOCR decay time constants could not be well approximated by a mixture of underlying time constants, but did include a 'long' decay time constant. '+/-' are the estimated standard deviations (see Appendix C.)

'Slow' onset time constants could be extracted even though the measurements recorded only 2.5 seconds of 'onset' and thus were not geared to detecting long onset time constants. Values for the 'slow' onset time constant ranged from 11 to 39 seconds. It was not possible to put an upper bound on all these estimates because the relatively brief MOCR elicitor, 2.5 s, did not allow us to sample enough of the curvatures. It was possible, however, to put a lower bound on all the estimates. Ear 130R produced a 'slow' time constant that had to be > 5.9 s and all other ears produced ones that had to be > 10.0s. The average 'slow' onset time constant estimate across ears was 24 seconds.

4. MOCR onset and offset delays both near 25 ms

Onset and offset delays were calculated from the 'sum of complex exponentials' characterizations (see Appendix C) and were generally between 15 and 40 ms (Figure 11). Ear 82L produced a 50 ms onset delay but this subject had a very low SNR and was the only subject for which the response did not entirely decay to zero, which complicated detecting response onset. In summary, the MOCR began to respond to an acoustic stimulus within 10's of milliseconds, and began to shut off just as quickly. Both the onset and offset delay were near 25 ms.

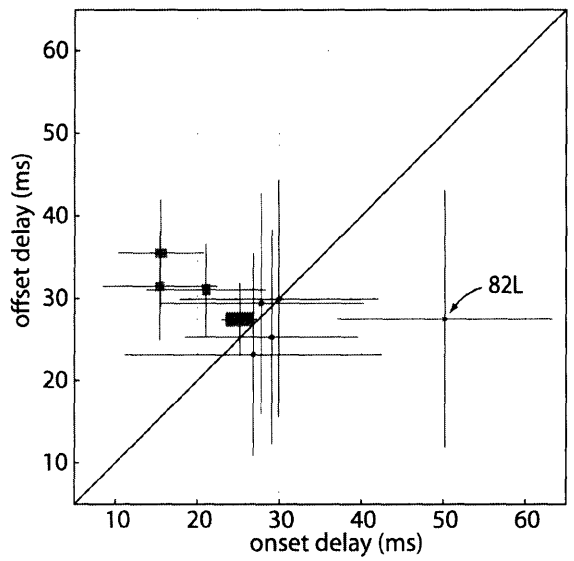


Figure 11. MOCR onset vs. offset delays for 9 ears show that both are near 25ms. Subject 82L's large onset delay value is probably a result of the this subject's response not completely decaying to zero between presentation intervals, see Figure 8. Error bars = 1 SD. To emphasize more accurate data points, i.e. those with small error bars, rectangles, whose areas represent relative accuracy, are centered on each data point (bigger area means more accurate).

5. A 2nd order model can describe the MOCR time-course

By comparing the parameters from the 'sum of complex exponentials' characterization with similar parameters from a simple second order system, it was found that a simple 2nd order model could largely account for the rising and decaying time-courses of the responses. Furthermore, the difference between the rising and decaying time-courses could be reproduced by changing the damping factor (the coefficient of the first derivative term) in that simple model by a factor of 2 while keeping all other model elements constant (see Appendix D).

B. MOCR time-course, elicitor level dependence

1. No systematic dependence of MOCR time-course on elicitor level

To investigate whether the MOCR time-course is affected by elicitor sound level, a second experiment was carried out on 4 of the original 9 ears using contralateral wideband noise elicitors at sound levels of 40, 45, 50, 55, and 60 dB SPL. Ears, 80L and 68R did not initially produce a measurable response at 40 dB SPL and further attempts to measure this level on those ears were abandoned.

Waveform curvatures were similar across elicitor levels for all four subjects (Figure 12, Figure 13). Ear 61R's overshoot was larger for larger elicitor levels both in absolute value and as a percentage of the maximum magnitude. In contrast, subject 68R had a constant percentage overshoot (8.6%). Neither the delays nor the MOCR time constants showed any systematic dependence on elicitor level (Figure 14).

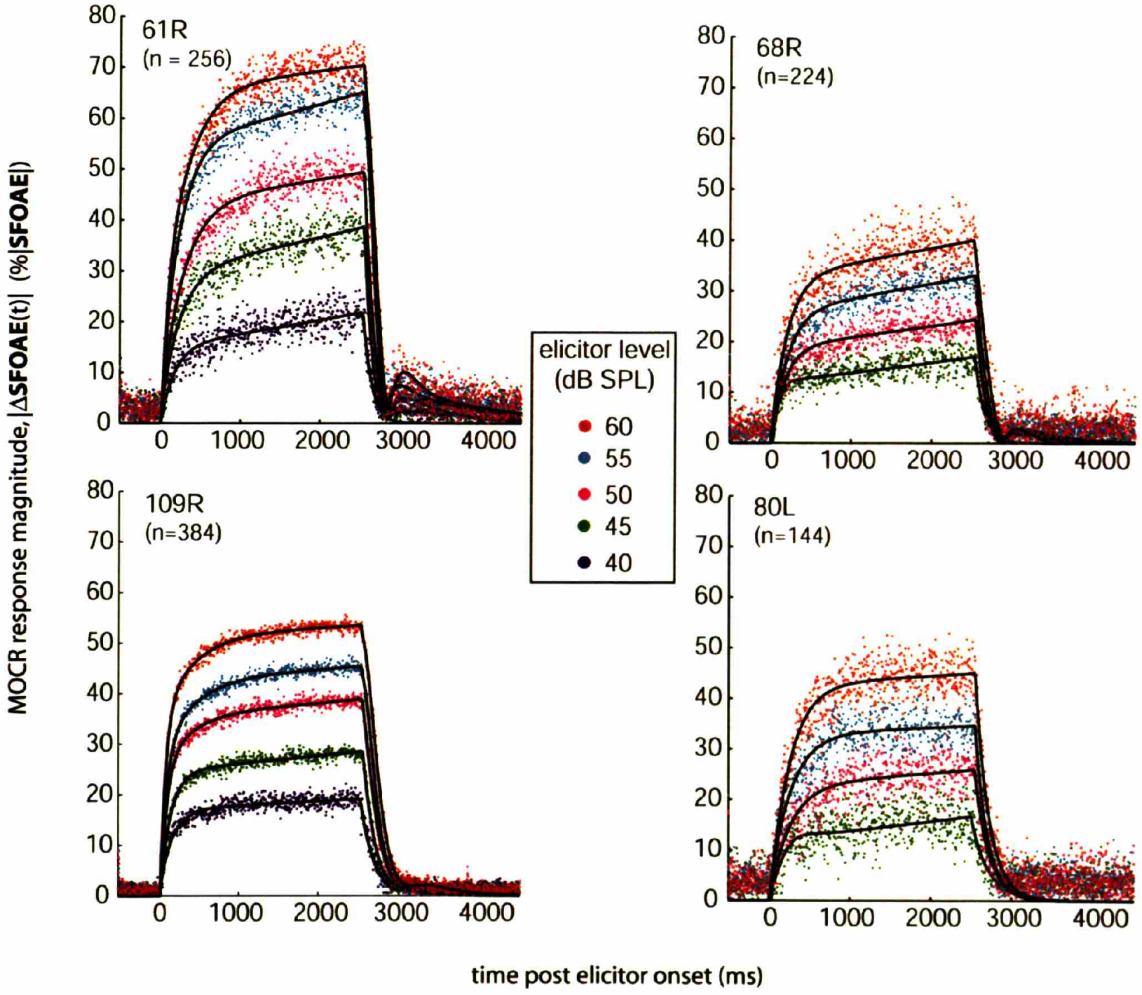


Figure 12. MOCR responses for wideband contralateral elicitors at various elicitor levels shows that responses were qualitatively similar across levels (4 subjects). Repetition interval was 5 sec and 'n' is the number of responses that were averaged for each measurement. Elicitor was on at 0 ms and off at 2500 ms. Solid lines are 'sum of complex exponentials' characterizations of the waveforms.

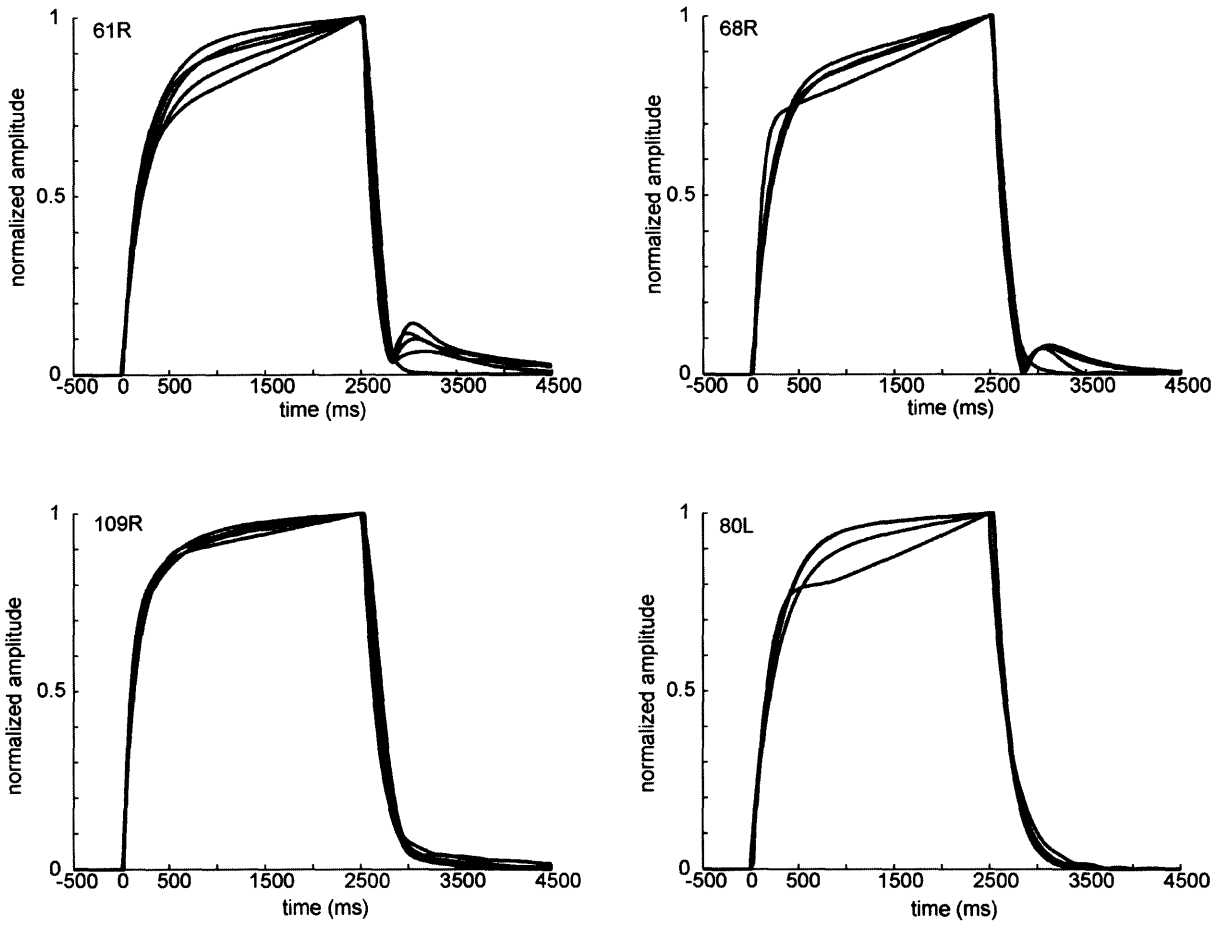


Figure 13. Normalized MOCR amplitude waveforms (maximum amplitude fixed to 1) for four subjects at different contralateral elicitor levels (overlaid) show similarity of the MOCR time-course across level. Each curve represents a different elicitor level (levels were 40,45,50,55,60 for 61R and 109R, and 45,50,55,60 for 80L and 68R). Subject 109R had the highest SNR and also presented the most consistent MOCR time-courses across level.

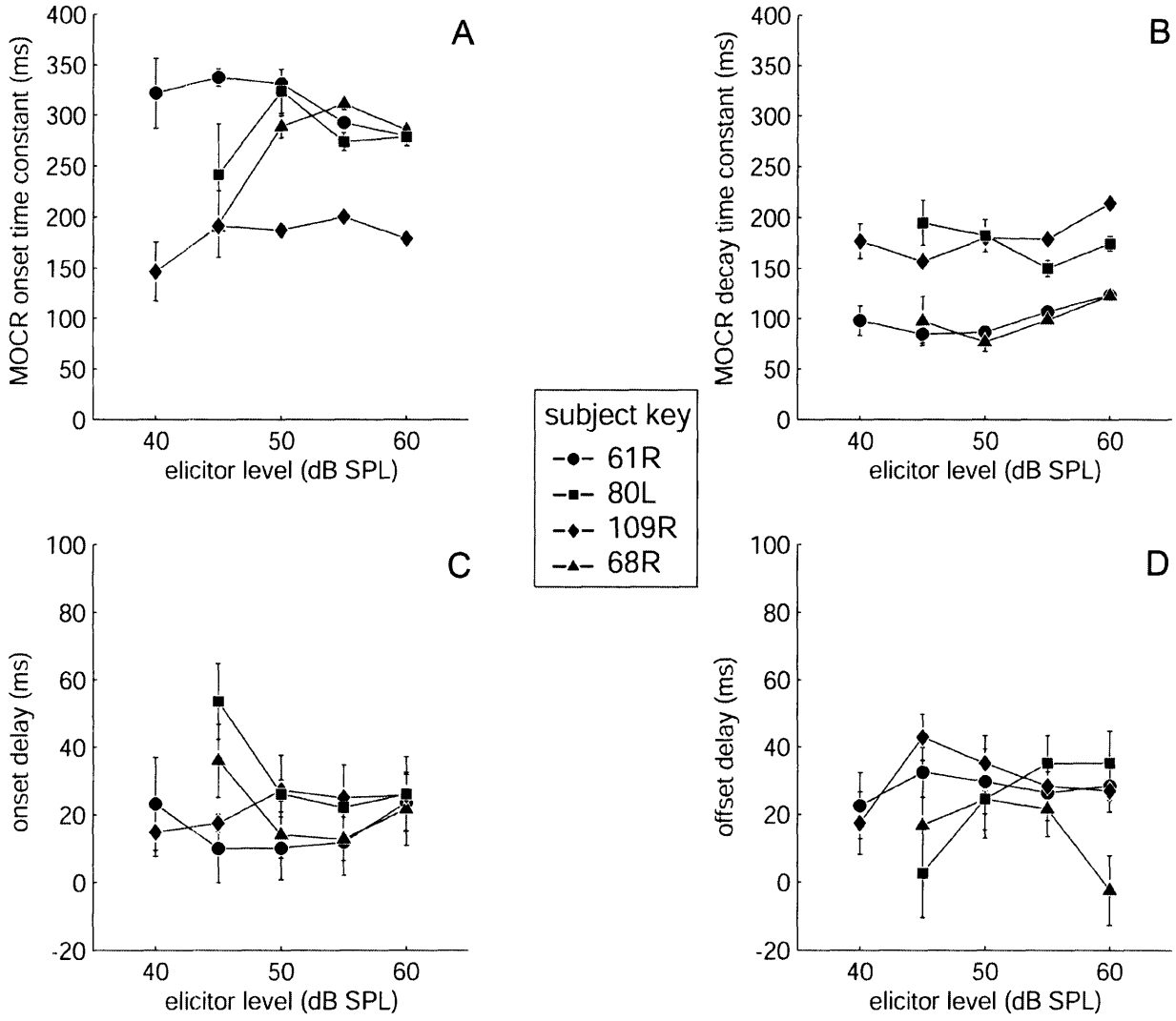


Figure 14. MOCR overall onset and decay time constants (panels A and B) and onset and offset delays (panels C and D) vs. contralateral elicitor level for 4 subjects show no systematic dependence on elicitor level. Error bars = 1 SD.

2. *MOCR growth function*

MOCR response amplitude increased in proportion to elicitor level almost linearly (at ~2% per dB SPL, Figure 15), over the elicitor range we sampled. Correlation coefficients (R values in Figure 15) from linear least squares regression for 3 of the 4 ears strongly suggested a linear relationship. Ear 61R had a slightly lower correlation coefficient. At the highest level, 61R produced the largest response of the group, one that departed from the linear trend. This could be an early sign of reflex saturation; perhaps for this ear the 60 dB SPL elicitor was beginning to maximally stimulate the reflex. Using higher level elicitors to determine the saturation point was not possible because of middle-ear-muscle activation.

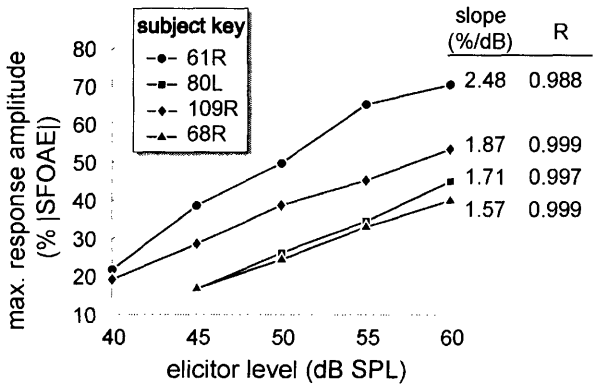


Figure 15. Growth function of MOCR, response amplitude vs. contralateral elicitor level shows an almost linear growth (correlation coefficient, R, from linear least squares regressions close to 1) with a slope of ~2% per dB SPL. Standard deviations are smaller than the symbols used to represent the data.

C. Time-courses of the ipsilaterally, contralaterally and bilaterally activated MOCR

To investigate the differences between ipsilaterally, contralaterally, and bilaterally activated MOCR time-courses, a third experiment was carried out on 3 of the original 9 ears. For this experiment, elicitors were presented ipsilaterally (re: the measurement ear), contralaterally, or bilaterally. Because activating the MOCR ipsilaterally or bilaterally requires that the elicitor be presented together with the probe-tone, we had to develop a stimulus that would minimize interactions (e.g. two-tone suppression) that caused non-MOCR mediated changes in the SFOAE. A 'notched-noise' elicitor was chosen. The notch, a 2.1 octave spectral notch centered at the probe-tone frequency, was designed to remove all energy at those frequencies that produced measurable two-tone suppression effects (Appendix E).

1. No systematic dependence of MOCR time-course on elicitor laterality

Ipsilaterally, contralaterally, and bilaterally activated MOCR responses produced waveform curvatures (Figure 16) for which neither the delays nor the single time constants showed any systematic dependence on elicitor laterality (Figure 17). Subjects 68R and 109R produced greater responses during contralateral activation than during ipsilateral activation; the opposite was true for subject 82L.

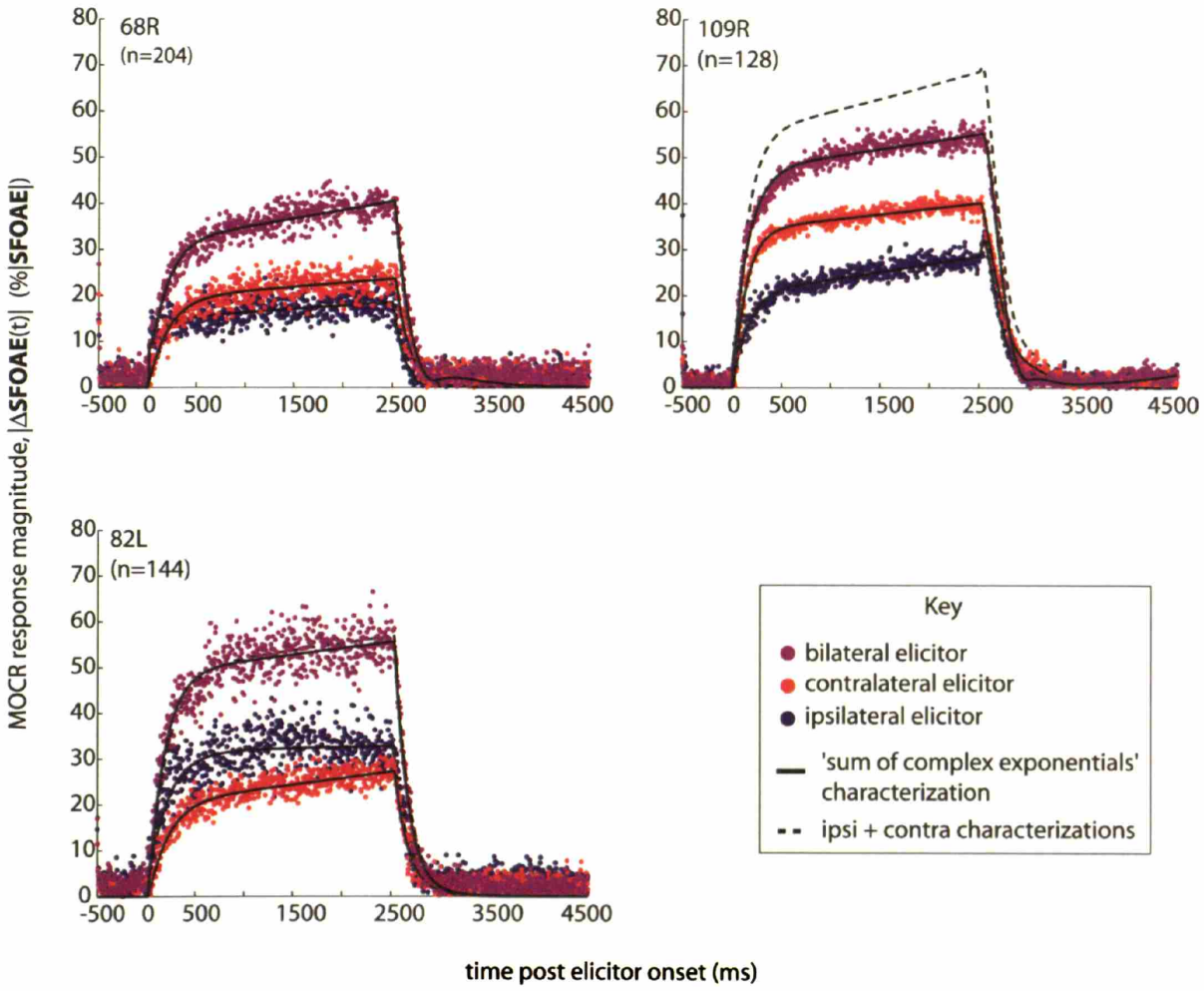


Figure 16. MOCR response waveforms for notched-noise elicitors presented ipsilaterally, contralaterally, and bilaterally in 3 subjects show that the waveforms were similar across laterality. Complex addition of the ipsilaterally and contralaterally activated responses (dashed lines) predicted the bilaterally activated response for subjects 68R and 82L, but not for subject 109R. Elicitor was on between 0 and 2500 ms, repetition interval was 5 s and 'n' is the number of responses that were averaged for each measurement.

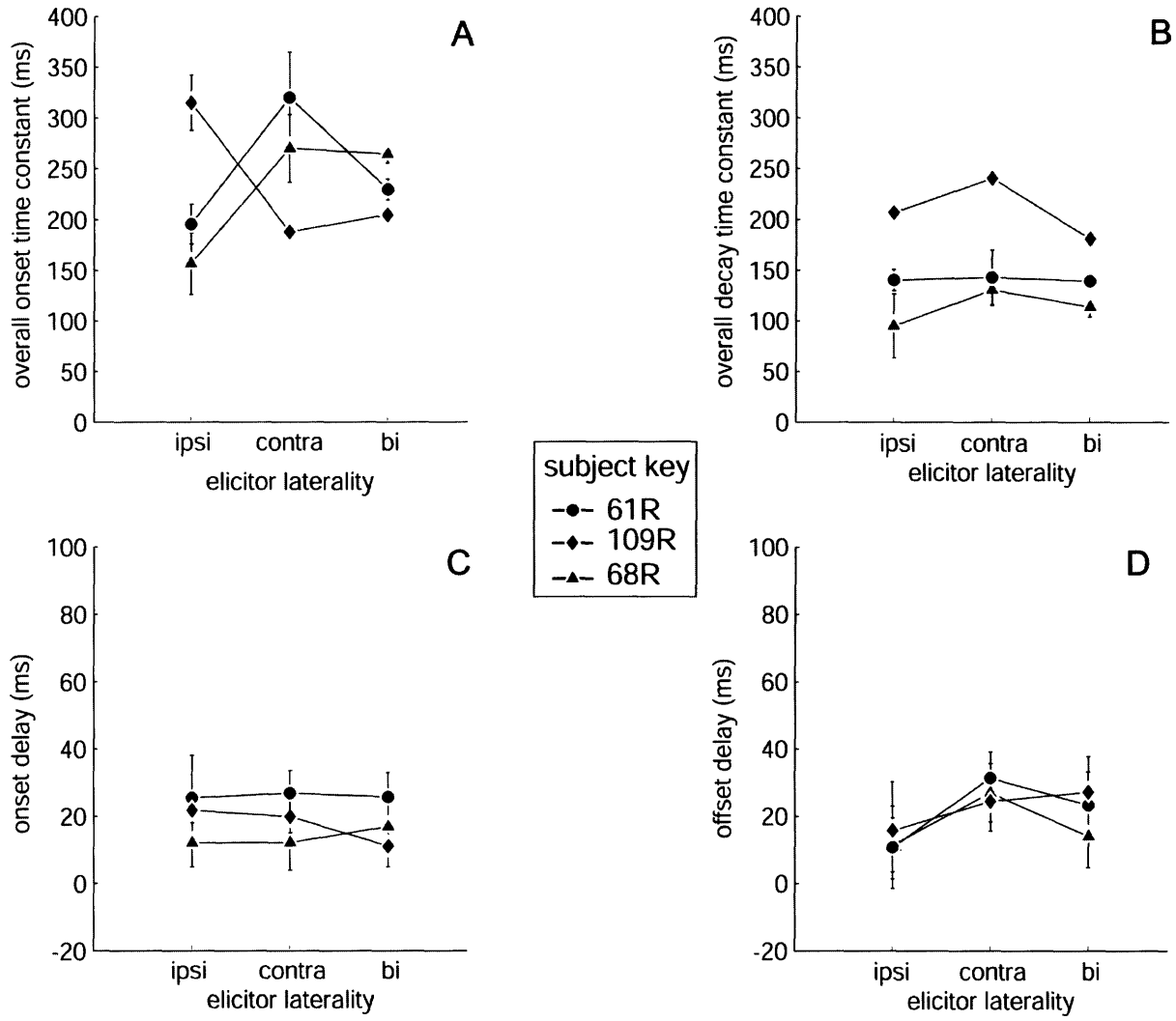


Figure 17. MOCR overall onset and decay time constants (panels A and B) and onset and offset delays (panels C and D) vs. elicitor laterality for 3 subjects show no systematic dependence on elicitor laterality.

2. *MOCR can exhibit binaural interaction*

How do the ipsilateral and contralateral limbs of the MOCR combine when activated together? One hypothesis is that the two effects add. To test this, we added the three-term characterizations of the ipsilaterally and contralaterally elicited responses (complex addition at each time point) and compared the result with bilaterally elicited responses. Two of three ears (68R and 82L) agreed with the hypothesis. Ear 109R, however, departed significantly from the hypothesis producing a lower bilateral response (by a factor of 0.8) and a greater phase (+20 degrees) than would be predicted by simple addition. Thus, 109R's measurement (but not during 68R's or 82L's) suggests binaural saturation or inhibition. This interaction could be due to neural processing (such as inhibition) and/or cochlear non-linearities. Although the magnitude of 109R's response was not predicted by the simple addition hypothesis, the 'shape' of this response on the complex plane was predicted by the simple addition hypothesis, and this was true for all three subjects.

IV. DISCUSSION

A. MOCR time constants

1. Onset time constants compared with previous work

We observed similar MOCR time-courses across all ears including similar, but not identical, overall onset (277 ± 62) and decay (159 ± 54 ms) time constants. The subset of ears that provided high SNR (4 of 9 ears) enabled us to probe the details of their time-courses which revealed (a) the existence of 3 underlying onset time constants, τ_{fast} = 60 – 80 ms, τ_{medium} = 290 – 350 ms, and τ_{slow} = 10's of seconds, and (b) that their responses decayed like a damped sinusoid with an overshoot—the damped sinusoid accounted for > 70% of the curvatures—but also included an exponentially decaying component with a long time constant, τ_{long} = 400 - 900 ms.

Previous data on the human MOCR time-course come from a variety of OAE measurements. Early data are accessible from a study investigating changes in spontaneous otoacoustic emissions (SOAEs) due to contralateral acoustic stimulation (CAS) (Mott, Norton et al. 1989). Here CAS-induced SOAE frequency shifts (which were more salient than concurrent amplitude changes) required 40 - 200 ms to reach 25% of their final value, corresponding to onset time constants of 139 - 695 ms, and consistent with our overall onset time constant values (Table 2).

Another MOCR time-course measure comes from the effects of CAS (30 dB SL, 80 or 244 ms duration wideband noise) on transiently evoked otoacoustic emissions (TEOAEs) (Maison et al., 2001). In this study, MOCR effects appeared to grow roughly linearly from 0 to 60 ms post CAS onset and then remain almost constant thereafter. This time-course is different from that found by other studies. The discrepancy may be due to limitations of the experimental method—the time-course was determined by moving 4 click probes to different times relative to the CAS onset—and the fact that the 60 dB SPL click stimulus used has been shown to also be an effective MOCR elicitor (Guinan et al., 2003).

The most extensive previous studies of the human MOCR time-course used distortion product otoacoustic emissions (DPOAEs). These studies measured changes in DPOAEs due to CAS or adaptation (Kim, Dorn et al. 2001; Bassim, Miller et al. 2003). DPOAE adaptation time-courses were fit with 2 exponentials: 1. One with a fast time constant, 10 ms < τ_{fast} < 350 ms, (median ~ 70 ms), and 2. One with a 'slow' time constant, 350 ms < τ_{slow} < 5.5s (medians 1.5 & 2.1 s from two studies). While the 70 ms time constant[15] matches our fast onset time constant (Table 2), the 1.5 to 2 s time constant is notably absent from our data. One explanation of this difference comes from a DPOAE adaptation study in cat where a ~1 s onset time constant was observed, but persisted after complete OCB section showing that it was mediated by intrinsic cochlear processes, not the MOCR (Liberman, Puria et al. 1996). Counter to this explanation, Bassim et al. (2003) reports roughly similar ~1 s time constants for changes in DPOAEs due to either CAS or adaptation.

Present in our data, but not noted in the DPOAE measurements are onset time constants of ~300 ms and ~10's of s. Kim et al., did observe a peak in their time constant histogram at the maximum obtained value of 5.5 s and suggested that longer stimuli and recording durations would be necessary to determine these time constants accurately. A similar comment can be made about our slowest onset time constants, τ_{slow} ~ 10's of s. Our fitting procedures showed that there were such time constants. We were able to put a lower bound, τ_{slow} > 5.9 ms, on the slow time constant that demonstrates it cannot correspond to the 1 - 2 s time constant reported in the DPOAE data (Liberman, Puria et al. 1996; Kim, Dorn et al. 2001; Bassim, Miller et al. 2003). Histograms of the time constants obtained via DPOAEs give hints of more peaks than the fast and slow time constants put forward by Kim et al. (2001) and Bassim et al. (2003). It seems likely that higher SNR DPOAE measurements would have revealed more details of the time-course, including more than two onset time constants.

Pursuing the MOCR time-course using DPOAE adaptation is like trying to appreciate a painting through a kaleidoscope; one must contend with unnecessary complexities, namely: (1) DPOAEs are composed of two underlying OAE sources with different properties (Shera and Guinan 1999) and they may behave differently under MOCR activation (2) A component of DPOAE adaptation can be mediated by intrinsic cochlear effects (i.e. not by the MOCR). These complexities can be observed in that DPOAE "adaptation" can cause both increases and decreases in the DPOAE level, and in that DPOAE-based measures of MOCR time constants produce wide scatter. Until these complexities are untangled, one

[15] 70 ms was the reported median, the average is larger due to significant scatter in the data.

cannot fully appreciate the MOCR time-course via a DPOAE adaptation method.

SFOAE-based methods are better suited to MOCR time-course investigation. They are able to measure the time-course in individual subjects, and are easier to interpret than those considered above because they require only a single low-level (40 dB SPL) probe-tone in the measurement ear, one that does not appear to activate the MOCR itself (Guinan, Backus et al. 2003). While a suppressor was used to normalize the data, and could be considered a complexity, normalization does not affect the time-course of the measurements.

We acknowledge several limitations of the present study. Specifically, the MOCR time-course reported here applies to wide-band noise elicitors (flat spectrum and notched). It is possible that other elicitors, e.g. narrow-band noise elicitors, tones, clicks etc., could produce different results[16]. Another limitation is that we used only noise elicitors of moderate to low levels. At high-levels, where the MOCR appears to afford protection from acoustic trauma (Rajan 1988; Maison and Liberman 2000; Rajan 2000), the time-course of efferent effects might be different. Finally, our study involved 9 ears where previous studies had > 20.

2. Onset time constants compared with cellular processes in outer hair cells (OHCs)

The fast (~70 ms) onset time constant

The fast (~70 ms) onset time constant we report was also found in many other cochlear measurements involving MOC activation: basilar membrane motion, otoacoustic emissions, cochlear microphonic, endolymphatic potentials, compound action potentials, and single auditory nerve fiber recordings, (Fex 1962; Desmedt, La Grutta et al. 1971; Warren and Liberman 1989; Cooper and Guinan 2003). Such universal presence indicates that the 70 ms time constant is a fundamental time constant of the MOCR.

Evidence for one possible cellular correlate for the ~70 ms time constant comes from measurements of the calcium (Ca^{2+})-mediated potassium (K^+) current found in OHCs (Housley and Ashmore 1991; Fuchs and Murrow 1992; Sridhar, Brown et al. 1997). Animal work on guinea pig isolated outer hair cells (OHCs) has shown that upon application of acetylcholine (ACh), an outward K^+ current develops with a time constant of 70 +/- 14 ms (Evans et al. 2000) but these measurements were done at room temperature and the actual K^+ current time constant at body temperature is likely to be faster. The K^+ current is a result of the change in intracellular calcium concentrations due to an influx of Ca^{2+} through MOC synapses. Could this be what gives rise to the universal ~70 ms time constant?

The medium (~330 ms) onset time constant

Ca^{2+} concentrations in the basal end of OHCs following the application of ACh have also been seen to increase on a ~300 ms time scale (Evans et al 2000) presumably through a different mechanism. It is possible that the ~330 ms time constant we report is related to Ca^{2+} release from local subsynaptic cisternae involving ryanodine receptors (Sridhar, Brown et al. 1997).

The slow (10's of s) onset time constant

Evidence of a slow (10's of s) onset time constant (Table 2) has been previously reported in guinea pig (τ_{slow} = 34 ± 9 s) (Sridhar, Liberman et al. 1995; Sridhar, Brown et al. 1997). In addition, a study on guinea pig basilar-membrane (BM) motion found that BM motion is inhibited by MOC activation on fast (10-100 ms) and slow (10-100 s) time scales and these data indicate that the slow effect has a different mechanical origin (Cooper and Guinan 2003) than the fast effect.

A possible OHC cellular correlate for τ_{slow} comes from the observations that (1) application of ACh to isolated OHCs results in a decrease of OHC axial stiffness on this time scale (~20 s), and (2) increases in intracellular Ca^{2+} causes the OHC cell body to elongate on this time scale (Sziklai, He et al. 1996; Dallos, He et al. 1997; Frolenkov, Mammano et al. 2003). The decrease in OHC stiffness appears to involve OHC regions far from MOC-OHC synapses. Presumably, the slow time constant is due to the time it takes for Ca^{2+} to migrate up the OHC[17] and affect the cytoskeleton.

OHC mechanisms may produce the majority of the observed MOCR time-course

[16] Superficially similar results were found using SFOAEs as probes and trains of clicks, tone pips, or DPOAE-evoking tone pairs as elicitors, but they were not analyzed by our current quantitative methods (Guinan, Backus et al. 2003).

[17] There is a system of Ca^{2+} stores (sub-surface cisternae) located along OHC lateral cell-membranes that could facilitate migration of Ca^{2+}.

Whether, the above postulated origins for these onset time constants are correct or not, the correspondence between the fast, medium, and slow time constants we measured and those found in OHCs suggest that OHC cellular processes could account for the majority of the MOCR time-course. Other possibilities do not look as promising. Post stimulus time histograms (PSTH) from recordings of single MOC neurons responding to tone bursts showed that MOC firing rate decreased over time (i.e. MOC neurons adapted) with a time constant of ~68 ms (Brown 2001). The MOCR effects we measured *increased* monotonically with continued stimulation, thus we did not see any effect of adaptation in our MOCR time-courses. The MOCR time-course we observed could conceivably be caused by recruiting more and more efferent fibers as the stimulus persists. However, since OHCs have been shown to have processes that evolve with time-courses similar to the MOCR time-course, a more likely explanation is that a majority of the time-course is generated downstream of MOC neurons.

B. Onset and offset delays

Our best estimates of onset and offset delays (i.e the time between elicitor onset or offset and a change in the observed response) put these values at ~25 ms for both. Previous studies found a large range of contralateral reflex latencies (Mott et al., 1989; Lind 1994; Giraud et al., 1997; Hill et al., 1997; Maison et al., 2001) though the methods used in these studies varied greatly in their ability to accurately detect the latency.

Our measured reflex delays can be divided into four components: (1) an acoustic delay[18] (2) A "neural" delay[19], defined as the delay from sound onset (or offset) to the firing (or decrease in firing) of MOC neurons at their OHC synapses. (2) MOC-OHC synaptic delay, which includes the delays within OHCs, and (3) reverse-otoacoustic delay, the delay for the MOC-induced change to appear as a change in the SFOAE in the ear canal. One theory puts the reverse-otoacoustic delay at approximately half of the overall SFOAE delay (Zweig and Shera, 1995) or ~5 ms (see Figure 18). The minimum neural delay in experimental animals is approximately 5 ms (reviewed by (Brown, de Venecia et al. 2003) and is probably near the same range for humans. In addition, the animal studies show that the latency of most neurons varies with sound level and is much longer than the minimum latency. Thus, there is at most 15 ms left for the MOC-OHC synaptic delay and the true synaptic delay is probably much less than 15 ms. There could be as little as only a few ms synaptic delay for MOC activity to begin to increase the flow of calcium into the OHC postsynaptic region and produce a measurable MOC effect.

Our experiments did not show that MOCR latencies were level-dependent as has been reported for individual MOC neurons (Brown 1989). Brown showed MOC neurons had latencies that decreased (60 ms – 10 ms) with increasing sound levels (0 - 10 dB re: neuron threshold, corresponding to 30 – 70 dB SPL) and averaged ~20 ms at high (>10 dB re: neuron threshold) levels. We observed ~25 ms over most levels. One explanation for the discrepancy (beyond the obvious animal vs. human, anesthetized vs. un-anaesthetized differences) is that our measure may not be sensitive enough to detect the earliest latencies from individual fibers but instead detects an aggregate latency, i.e. when 'enough' fibers come online to make a detectable change. If this were true, we might not expect to see level dependence because our stimulus levels started at 40 dB SPL, a level loud enough to put many of the fibers in their non level-dependent ~20 ms regime. Another possibility is that the low accuracy of our latency estimates (SDs averaged ~15 ms) combined with the small range of levels tested, spanning 20 dB SPL, prevented us from detecting an existing level-dependence.

C. MOCR time-course may be governed by a 2nd order system.

Both the onset and decay of MOCR responses can be fit to a 2nd order system; and only one system parameter needs to be changed to account for the elicitor-on/elicitor-off difference (Appendix D). The onset time-course, by itself, can be produced by separate, single-time-constant processes. The decay time-course, on the other hand, shows an overshoot like a decaying sinusoid that cannot be produced by separate, single-time-constant processes. The finding that a 2nd order system can account for 70-90% of both time-courses (Table 2 and Appendix D) by allowing one parameter to change by a factor of 2 is evidence that the MOCR's onset and decay are governed by the same 2nd order system. In short, one system can account for the bulk of the time-course,

[18] Time '0' was when the elicitor stimulus's electrical signal was sent to the sound source. Acoustic delays are < 0.1 ms.
[19] The 'neural' delay contains both forward-otoacoustic and neural delays. One reason these two delays are combined is because it is hard to calculate what the forward-otoacoustic delay should be for a wideband stimulus—delays in the cochlea are different for different frequencies.

giving rise to the two faster onset time constants as well as the decay overshoot. Considering the similarity of the MOCR time constants with those from various OHC measurements, this 'one system' seems likely to be in OHCs.

D. Time-course evidence for binaural interaction

Two of three subjects produced bilaterally activated MOCR responses that were well approximated by the sum of the ipsilaterally and contralaterally activated responses, i.e. they showed no binaural interaction of the reflexes (Figure 16). In contrast, ear 109R produced a lower bilateral response than the sum of the unilateral responses, indicating a binaural inhibition. Possible sources for this binaural inhibition include central reflex inhibition and/or a saturation of the MOC effect in the periphery. The Chapter 2 study using 24 subjects showed there was no prevailing binaural facilitation or inhibition.

Binaural interactions that were a function of elicitor interaural time difference have been recently reported (Kemp, Hsueh et al. 2005). Our experiments used the same elicitor noise in both ears and therefore could not detect binaural interactions that required different signals in the two ears.

E. Implications of the MOCR time-course for the role of the reflex in hearing

The human MOCR's time-course is best suited to operate on acoustic changes that persist for 100's of ms or longer. This conclusion is based upon the fact that overall MOCR effects in the cochlea build up and decay over a time scale of 100's of milliseconds. Time constants of 10's of seconds are also present. Consequently, MOCR is not fast enough to be operating on the information-carrying envelope of speech or to provide any protection from isolated loud impulse noises, such as gunshots. The time-course is, however, consistent with other roles that have been postulated for the MOCR: protection (from long-lasting, > 100 ms loud sounds) (Rajan and Johnstone 1983; Reiter and Liberman 1995), dynamic range adjustment (Geisler 1974; Winslow and Sachs 1988), signal detection in noise (Winslow and Sachs 1988; Kawase, Delgutte et al. 1993), and aiding selective attention (Hernandez-Peon 1956; Meric and Collet 1994).

The MOCR and the MEMR respond differently to increasing acoustic elicitor levels. MEMR response onset latencies and onset time constants decrease with increasing elicitor level (Moller 1961), but MOCR offset latencies and decay time constants depend very little on elicitor level (Figure 14). In addition, MEMR responses wane in the presence of continuing low-level elicitors, but do not adapt for high-level elicitors (Dallos 1964). These MEMR time-course properties are useful for a reflex serving a protective role, perhaps the primary role of the MEMR. The MOCR time-course, on the other hand, shows little or no dependence on elicitor level (Figure 13). In other words, over the measurable range of elicitor levels for both reflexes, there is a fundamental difference in the way the two reflexes respond to increasing elicitor levels. This difference broaches the possibility of different primary functions for the two reflexes.

The pupillary light reflex is similar to the MOCR in that it operates over 100's of milliseconds[20]. The function of the pupillary light reflex is to adjust the amount of light entering the eye in order to optimize visual acuity (Campbell and Gregory 1960). Perhaps the MOCR does a similar thing for sound and the ear.

APPENDIX A: MIDDLE EAR MUSCLE TEST

The middle ear muscle reflex (MEMR) is a sound-evoked reflex that can produce changes in the ear canal sound pressure, $\Delta\mathbf{C}(t)$, that are superficially similar to those produced by the MOCR. MEMR-induced changes in $\Delta\mathbf{C}(t)$ result from middle-ear muscle contractions changing the mobility of the middle ear and consequently changing the acoustic probe-tone stimulus in the ear canal (see Figure 7). In order to keep the probe-tone component invariant such that $\Delta\mathbf{C}(t)$ provides a measure of $\Delta\mathbf{SFOAE}(t)$ exclusively, elicitor levels below the MEMR threshold must be used.

To insure that our elicitor levels were low enough, we used a phase-slope[21] test. When MEMR effects are present, phase-slopes (slope of $\angle\Delta\mathbf{C}(t)$ vs. probe-tone frequency) are either not well defined or are close to 0 ms (Guinan, Backus et al. 2003). For this test, the phase of $\Delta\mathbf{C}(t)$ in response to a 60 dB SPL broadband elicitor was measured for 4 or more probe-tone frequencies (in 20 Hz spacing near 1 kHz) and phase-slopes were calculated (Figure 18). A consistent slope between 6 and 15 ms was taken as evidence that the source of the changes was the MOCR and not the

[20] The time-course of the pupillary light reflex, however, depends on light stimulus intensity, and color.

[21] This phase-slope is conventionally referred to as "group delay." Group delays are readily interpretable for linear systems, where different frequencies never interact; for non-linear systems, such as the ear, the interpretation of the term "group delay" is complicated.

MEMR because such slopes indicate a round trip to the inner ear (near the ~1 kHz probe-tone frequency place) where MOCR effects manifest. In this study, all ears were free from measurable MEMR effects at elicitor levels of 60 dB SPL.

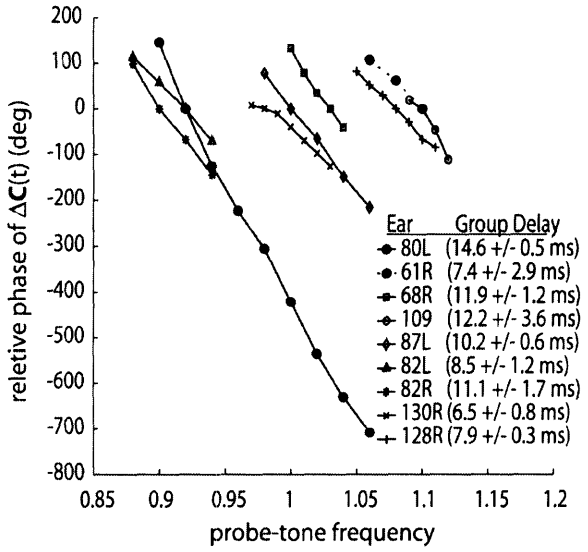


Figure 18. MEMR phase-slope tests for the 9 ears in this study. All ears produced definable phase-slopes between 6 - 15 ms, indicating that the measured changes in ear-canal sound pressure at these elicitor levels (elicitors were bilateral wideband 60 dB SPL noise bursts) were predominately mediated by the MOCR. Each point represents the average phase in a post-elicitor window (between 2550 ms and 2650 ms) of the change in the ear canal sound pressure at one probe-tone frequency, C(t). Slopes were calculated using linear regression. Standard deviations were calculated via bootstrapping.

Since middle ear muscle responses are graded; this test does not insure zero middle ear muscle effects, but rather shows that the observed measurement does not have MEMR effects that are large enough to capture the phase of the sound-induced change in the ear canal sound pressure.

APPENDIX B: MEASUREMENT NORMALIZATION

SFOAE-based MOCR measurements produce low-amplitude responses when the SFOAE has a low-amplitude; however, MOCR strength is not necessarily weak in these cases. To compare MOCR strengths across measurements with varying SFOAE amplitudes,[22] we report responses in units relative to the amplitude of the SFOAE being monitored;

$$|\Delta\mathbf{SFOAE}(t)| = \frac{|\Delta\mathbf{C}(t)|}{|\mathbf{SFOAE}|} \qquad \text{(B1)}$$

To determine $|\mathbf{SFOAE}|$ we suppressed the SFOAE via two-tone suppression. Ideally, if suppression of the SFOAE is complete, the amplitude of the vector difference in EC sound pressure between the suppressed and non-suppressed conditions would equal the native SFOAE amplitude (i.e. $|\Delta\mathbf{C}| = |\mathbf{SFOAE}|$). We used a 60 dB SPL ipsilateral suppressor-tone stimulus 110 Hz below the probe-tone to suppress the SFOAE. This tone did not completely suppress the SFOAE (see Appendix E for more details) but gave a good approximation. $|\mathbf{SFOAE}|$ was taken to be the average change in EC sound pressure amplitude caused by the suppressor-tone (the average $|\Delta\mathbf{C}(t)|$, see Figure 19). The $|\mathbf{SFOAE}|$ estimate was stable and repeatable across sessions and days even though the pre-suppressor baseline wandered. In other words the SFOAE rode on baseline variations (Figure 19).

[22]Normalization is important when investigating the dependence of the MOCR strength on sound level across subjects.

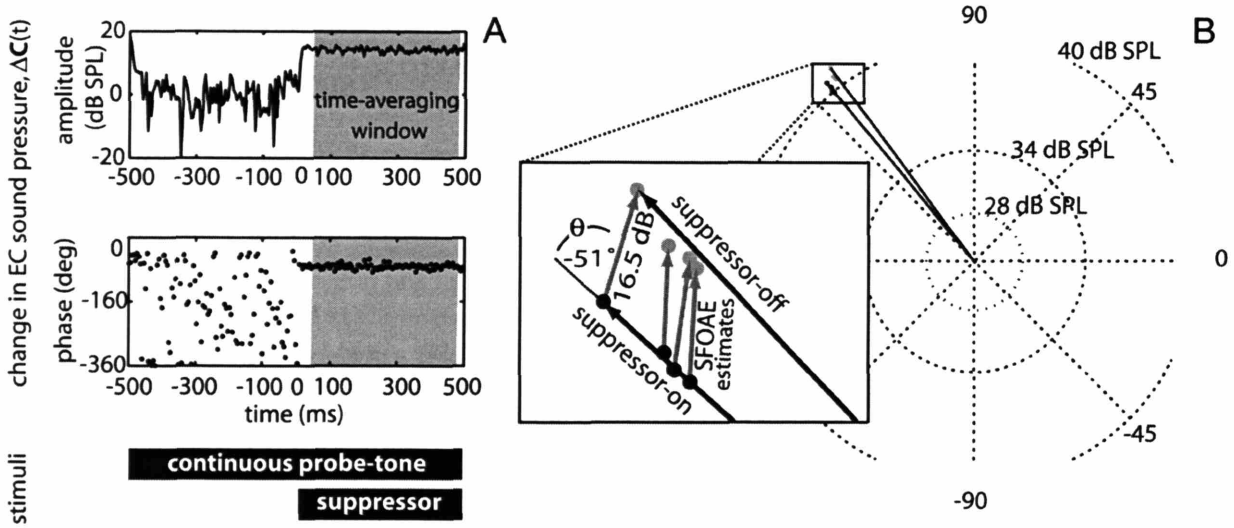
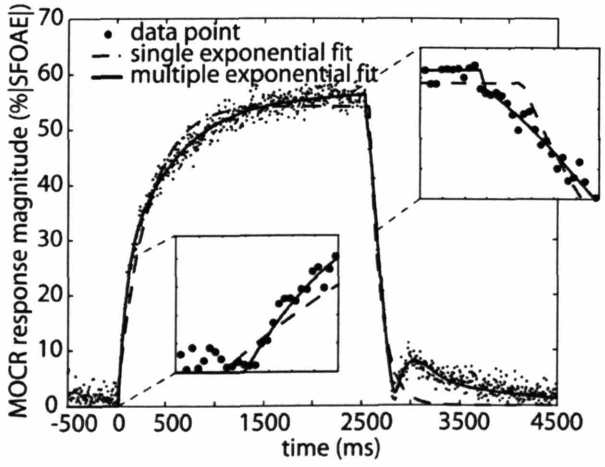


Figure 19. Panel A shows how the change EC sound pressure (relative to the average pre-suppressor EC pressure across t = -450 to -50 ms) during a two-tone suppression measurement is used to estimate an SFOAE amplitude. Vector time-averaging the change in EC sound pressure due to the suppressor-tone (i.e. across shaded region, 50 to 450 ms) produced an estimate of the native SFOAE. Panel B shows the repeatability of the estimate of SFOAE by plotting 4 such SFOAE estimates (grey vectors) made at different times for the same subject, ear, and probe-tone frequency. The SFOAE vector labeled '16.5 dB SPL' in panel B was obtained from the measurement shown in panel A. The raw suppressor-off and suppressor-on vectors (from time averaging over the same shaded window prior to subtraction, and not shown in panel A) are also shown. Stimulus parameters were: probe-tone frequency = 1.04 kHz, probe-tone level = 40 dB SPL, suppressor-tone frequency = 930 Hz, suppressor-tone level = 60 dB SPL, subject 87L.

APPENDIX C: MATHEMATICAL CHARACTERIZATIONS OF THE MOCR RESPONSE WAVEFORM

In order to quantify the MOCR responses, two mathematical characterizations were made for each waveform (Figure 20). First, 'single complex exponential' characterizations were made to quantify MOCR time constants for the rising and decaying portions of each response. Second, 'sum of complex exponentials' characterizations were made to quantify onset and offset delays, extract multiple time constants (when possible), and to describe the rising and decaying curvatures more accurately. Complex exponentials were always used because these produced curvatures similar to the measured responses and because complex terms could fit magnitude and phase data simultaneously[23].



[23] This strategy removes the bias that is introduced when fitting the magnitude data alone. This bias can be understood by realizing that when noise exists in a complex-valued measurement, (zero mean noise in x and y) the resulting magnitude is always > zero. Therefore, an estimate of the magnitude of the signal based on only magnitude data will be biased by the noise (that produces a magnitude itself); and the amount of the bias will depend upon the level of noise in the measurement.

Figure 20. Two characterizations of the MOCR time-course evoked by contralateral sound. Data (points) show MOCR mediated change in the SFOAE induced by a 60 dB SPL contralateral wideband noise elicitor (on at 0 ms and off at 2500 ms). The two curves represent two mathematical characterizations of the data: a fit using a single complex exponential term for the rising and decaying portions (dashed) and one using 3 such terms for each portion (solid). Exploded views show transition regions. Since the rising and falling portions were fitted separately, 'jumps' (less than the measurement noise) could occur (ear S61R, test tone 1.1 kHz, 816 averages).

1. Single complex exponential characterization

For the 'single complex exponential' characterization a piecewise continuous function $\mathbf{y}_1(t)$ (Eq. C1) with 5 free parameters ($t_r, \mathbf{Z}_r, \mathbf{s}_r, t_d$, and $\mathbf{s}_d$) was used to characterize each response waveform, **ΔSFOAE**(t).

$$\mathbf{y}_1(t) = \begin{cases} t < t_r \;\; , \; \mathbf{y}_0 = 0 + 0i \\ t_r \le t \le t_d \;\; , \; \mathbf{y}_r(t) = \mathbf{Z}_r(1 - e^{\mathbf{s}_r(t-t_r)}) \\ t_d < t \;\; , \; \mathbf{y}_d(t) = \mathbf{Z}_d e^{\mathbf{s}_d(t-t_d)} \\ with \;\; \mathbf{Z}_d \; set \; to \; \mathbf{y}_r(t_d) \end{cases} \quad \text{(C1)}$$

Where:

t_r = time when the response onset begins (re: elicitor onset, i.e. the onset delay)

t_d = time when the response offset begins (re: elicitor *onset*)

$\mathbf{s}_r$ = complex exponent of the rise[24]

$\mathbf{s}_d$ = complex exponent of the decay

$\mathbf{Z}_r$ = eventual (saturated) maximum (complex-valued)

$\mathbf{Z}_d$ = complex value from which the decay begins (not a free parameter, determined by $\mathbf{Z}_r$, $\mathbf{s}_r$, and t_d)

[24] For a single term complex exponential, the complex-valued exponent can be thought of in its component parts. The real part of the exponent is inversely related to the a conventional time constant and so determines the speed with which the magnitude changes over time while the imaginary part is related to the speed with which the phase changes over time.

All parameter values were determined simultaneously using a non-linear parametric least-squares search algorithm that minimized the error between $\mathbf{y}_1(t)$ and a response waveform, **ΔSFOAE**(t). From this 'single-complex-exponential' characterization, single onset and offset time constants were calculated (Eq. C2 and C3).

$$\tau_r = -1/\mathrm{Re}\{\mathbf{s}_r\} \quad \text{(C2)}$$

$$\tau_d = -1/\mathrm{Re}\{\mathbf{s}_d\} \quad \text{(C3)}$$

2. 'Sum of complex exponentials' characterization

For the 'sum of complex exponentials' characterization, the piecewise function, $\mathbf{y}_2(t)$, (Eq. C4) was used to characterize each response waveform, **ΔSFOAE**(t).

$$\mathbf{y}(t) = \begin{cases} t < t_r \;\; , \; \mathbf{y}_0(t) = 0 + 0i \\ t_r \le t \le t_d \;\; , \; \mathbf{y}_r(t) = \mathbf{Z}_{DC} + \sum_{n=1}^{2 \, or \, 3} \mathbf{Z}_{rn}(1 - e^{\mathbf{s}_{rn}t}) \\ t_d < t \;\; , \; \mathbf{y}_d(t) = \sum_{n=1}^{2 \, or \, 3} \mathbf{Z}_{dn} e^{\mathbf{s}_{dn}t} \end{cases}$$

Eq. (C4)

The number of terms (and therefore parameters) was determined by an algorithm[25]. The roles of the parameters in this characterization are analogous to those in the 'single complex exponential' characterization described above except: 1. The real and imaginary parts of the complex exponents cannot necessarily be separated when being interpreted (e.g. complex conjugate exponents add to form sinusoids[26]). 2. The eventual maximum value of the response is represented by the sum of $\mathbf{Z}_{rn}$ and a

[25] The number of parameters was increased until the least squares fit failed to improve or did so only incrementally. Higher SNR measurements produced more terms. The maximum number of parameters generated was 14. This happened for the 4 highest SNR subjects: 87L, 109R, 68R and 61R, who's rising and decaying response curvatures were described by the sum of 3 complex exponential terms.

[26] No restrictions were placed on the parameters; consequently, the functions may defy interpretation as combinations of familiar functions.

constant, $\mathbf{Z}_{DC}$. 3. $\mathbf{Z}_{dn}$ act in aggregate without a constant.

To carry out each characterization, the waveform was split into three regions: a) pre-response, in which the response was considered to be zero. b) rising response (including the plateau), and c) decaying response. Every data point was ascribed to one of the three regions. Two time-boundaries, t_r and t_d, were chosen in order to separate the regions (this was re-done for all reasonable t_r, t_d pairs). For each t_r, t_d pair, all remaining parameters in each region were determined by using a matrix pencil method (Hua 1990; Sarkar 1995). The parameters of the rising portion were not constrained to make the **y**(t) curve go though the point 0+0i. Neither were the rising and decaying portions of the characterization constrained to coincide. When discontinuities appeared at these boundaries they were within the measurement noise.

The number of terms to use was determined by a 'cost/benefit' approach. Terms were added, $\mathbf{Z}_{rn}(1-e^{\mathbf{s}_{rn}t})$ for the rising region or $\mathbf{Z}_{dn}e^{\mathbf{s}_{dn}t}$ for the decaying region, until the additional term failed to improve the goodness of fit (R^2 value) in that region or did so only incrementally[27]. Once the optimal number of terms and the associated parameter values were determined for each region, the three regions (i.e. the rising, falling, and the pre-elicitor region assumed to contain no signal) were conjoined to form a curve. The 'fit' between the resulting composite curve, **y**(t), and the entire response waveform being characterized, **ΔSFOAE**(t), was evaluated using the standard goodness of fit value, R^2, evaluated over all three regions. The process was repeated for all reasonable t_r / t_d pairs, and the **y**(t) curve that gave the highest R^2 value was selected as the winning 'sum of exponentials' characterization (this included the t_r and t_d parameters that segregated the winning curve as well as the associated parameters determined from the matrix pencil method: $\mathbf{Z}_{rn}, \mathbf{s}_{rn}, \mathbf{Z}_{dn}, \mathbf{s}_{dn}$)

The 'sum of exponentials' characterization was used to extract multiple time constants where possible. Conventional time constants are defined by real-valued exponents but our exponents were complex-valued. Consequently, the calculation of multiple conventional time constants was complicated by interactions between $\mathbf{s}_{rn}$ or $\mathbf{s}_{dn}$ terms. However, if the imaginary parts of the parameters were small relative to their real parts (i.e. the exponents were mostly real), multiple time constants were approximated as:

$$\tau_{rn} = -1/\mathrm{Re}\{\mathbf{s}_{rn}\} \qquad \text{(C5)}$$

$$\tau_{dn} = -1/\mathrm{Re}\{\mathbf{s}_{dn}\} \qquad \text{(C6)}$$

In order to quantify onset and offset delays with greater time resolution than our sample rate (5ms/point), onset and offset delays were calculated from the winning 'sum of exponentials' characterization. The response onset time (the time of earliest MOCR response after elicitor inception) was determined by the time of intersection, or the time of nearest miss when there was no intersection[28], of the rising portion of the characterization and 0+0i. The response-offset time was similarly determined by the time of intersection, or the time of nearest miss when there was no intersection, of the rising and decaying portions of the characterization. The onset delay and the offset delay were then calculated by subtracting elicitor onset and offset times from response onset and offset times respectively.

3. Calculating the best estimates of parameters and estimating their errors

To provide the best estimate for each parameter and to quantify the error of those best estimates, two simulations were done for every waveform characterized. The first simulation was used to quantify the error caused by measurement noise; the second simulation was used to quantify biases introduced by the characterization process.

The first simulation calculated means and variances at each time point prior to averaging across trials. These statistics were used to define independent

[27] Over-fitting manifested when sinusoidal oscillations appeared in the characterization curves. Such oscillations were obvious in the curves when they occurred, and were not present in the data. These oscillations were excluded to insure smooth curves and their exclusion set an upper bound of 3 on the number of complex exponential terms that could be used in the characterization.

[28] The parameters of the rising portion were not constrained to make the **y**(t) curve go though the point 0+0i. Neither were the rising and decaying portions of the characterization constrained to coincide. When discontinuities appeared at these boundaries they were within the measurement noise.

Gaussian distributions[29] at each time point from which new samples could be picked. By sampling from each time point's distribution 500 times, 500 waveforms that were statistically similar to the original waveform were generated. These 500 waveforms were mathematically characterized in the same way as the original response waveform, and they produced 500 estimates for each parameter so that each parameter had a distribution.

The second simulation added noise taken at random with replacement from a subject's pre-elicitor response region (-450 to -50 ms) to a signal with preset parameters. 500 waveforms were made this way; these produced 500 estimates of each known parameter. The known parameter values were then subtracted from the estimates to reveal any statistically significant bias. This analysis showed that onset and decay time constants were free from significant bias, but that onset and offset delays were underestimated by 0 - 10 ms depending on the noise level.

The distribution of values of a parameter from the first simulation was convolved with the bias distribution from the second simulation. The resulting distribution was used to obtain the best estimate for that parameter (the distribution mean) and the standard deviation of the best estimate (the distribution standard deviation)[30]. These are the values reported in this manuscript.

APPENDIX D: A SIMPLE PHENOMENOLOGICAL MODEL FOR THE MOCR REPONSE

Although the rising time-course of the MOCR response appears fundamentally different in shape than its decay, a simple model shows how the main features of both time-courses may be due to the same underlying system. To better understand how these time-courses might be connected, we attempted to model both using a simple 2nd order system, Eq. (D1). Symbols appropriate for a mechanical system were used but the actual underlying system is more likely neuro-chemical.

$$M\ddot{x}(t) + B\dot{x}(t) + Kx(t) = F_{in} \qquad \text{(D1)}$$

$$x(t) = \mathrm{Re}\{\frac{1}{2} \cdot \sum_{n=1}^{2} e^{\mathbf{s}_n t}\} \qquad \text{(D2)}$$

The displacement time waveform of Eq. (D1), $x(t)$, in response to a step displacement input can be found by invoking a Laplace transformation and solving which gives Eq. (D2). The system's behavior is determined by the parameters M, B, and K or equivalently by the loci of the complex-valued 'poles' ($\mathbf{s}_1$ and $\mathbf{s}_2$ after solving for $\mathbf{s}$ or the roots of Eq. D1.). If the poles lie on the real axis, pure exponential curvatures exist; if the poles are complex conjugates, a sinusoidal component exists. The intensity independency of the time-course means that multiplication of Eq. D1 by any constant will continue to produce the same time-course, therefore it is the ratios of the parameters that determine the time-course thus the problem can be reduced to two parameters K/M and B/M.

The loci of 4 sets of $\mathbf{s}_{r_n}$ and $\mathbf{s}_{d_n}$ parameters (see Appendix C) from the 'sum of exponentials' characterizations of our 4 highest SNR MOCR responses were compared with the loci of $\mathbf{s}_1$ and $\mathbf{s}_2$ poles from the simple 2nd order model (Figure 21). With M and K fixed (M = 100 kg and K = 0.0065 N/m) we matched the locations of the rising $\mathbf{s}_{r_n}$ parameters with a B value of 2 Ns/m. Keeping M and K at their fixed values, we closely matched two of the three[31] $\mathbf{s}_{d_n}$ parameters solely by reducing B by a factor of two to B = 1. Thus, for these subjects, the transition from the rising curvature to the decaying curvature can be largely achieved by changing a single parameter (the first derivative coefficient) in a 2nd order model. This suggests that a single second order process rather than multiple unconnected processes are largely responsible for the MOCR's time-course.

[29] Real and imaginary parts were treated as independent Gaussian distributions and were well-approximated by this assumption.

[30] This is an over-estimate of the standard deviation because both simulations used measurement noise, (albeit different types). Measurement noise only appears once in the actual data.

[31] The third decay parameter $\mathbf{s}_{d3}$ represented a long exponential time constant that was not captured by this model. It was ignored because it accounted for <30% of the decay curvature.

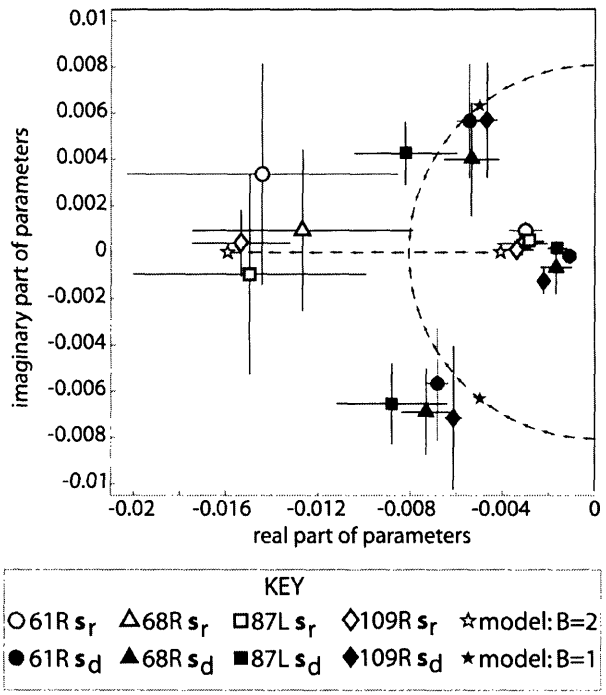


Figure 21. Exponent parameters or poles for data from four ears that had high SNR compared with the poles of a simple second order model (for an explanation of parameters see Appendix C). The rising portion of the responses (unfilled symbols) were well characterized by two real 'poles' with two corresponding time constants. The decaying portion of the responses (filled symbols) were well characterized by 2 complex conjugate poles (accounting for > 70% of the decay curvature) plus a single real pole with a long time constant. The dashed lines with arrows show how the two poles of a simple second order system move when the value of the damping element is changed from 0 to 2 (while keeping chosen mass and spring elements constant: M = 100 kg., K = 0.0065 N/m). Particular pole locations for two values of the damping element are designated by stars. The bulk of the observed wave-shapes can be accounted for by changing a single parameter, the damping element (or first derivative coefficient) in a simple second order model. Open symbols are onset poles and filled symbols are decay poles and different symbol shapes are used for different ears as shown in the key.

The agreement between these data and the simple 2nd order model is not perfect. The 'conjugate poles' were not true conjugates in the sense that they did not form a vertical line and in that they did not have equal weighting (generally the term with the lower pole had a larger coefficient magnitude). And the data constellations did not strictly overlay the 2nd order system's path (dashed line in Figure 21). Nonetheless, the model provides a good approximation to the measured data and shows that much of the difference between the rising and falling time-courses can be accounted for by a single underlying 2nd order system.

APPENDIX E: TWO-TONE SUPPRESSION BANDWIDTH

Measuring ipsilaterally or bilaterally activated MOCR responses using our SFOAE-based method required a probe-tone and an elicitor-noise be presented simultaneously in the measurement ear. In this situation, two-tone suppression mechanisms can reduce the SFOAE amplitude, obfuscating MOCR responses. To avoid such contamination of our MOCR responses, we used an elicitor-noise with a spectral notch centered at the probe-tone frequency. The notch width was designed to be wide enough to not produce two-tone suppression effects. To determine the appropriate notch width, we measured the bandwidth of two-tone suppression of the SFOAE (Figure 22)[32]. For these measurements, a 40 dB SPL probe tone was fixed at a subject's probe frequency (near 1 kHz) while a 60 dB SPL suppressor-tone was presented at various frequencies (21 logarithmically spaced frequencies spanning 3 octaves and centered at the probe tone frequency were used). Since the MOCR does not respond well to pure tone stimuli (Guinan, Backus et al. 2003) as demonstrated in Figure 22 by the lack of any effect of contralateral 'suppressor-tones' (dashed lines), all resulting changes in the SFOAE from adding ipsilateral tone suppressors were presumed to be to non-MOCR, two-tone suppression effects. The bandwidth of suppression was found to be ~2.1 octaves.

[32] Our standard suppression measurement used to estimate |**SFOAE**| and give y-axis normalization of MOCR responses uses a suppressor tone presented 110Hz below the probe frequency. However, the excellent cancellation afforded by alternating elicitor polarity rendered this offset unnecessary and created a situation where a suppressor tone presented nearer or even at the probe tone frequency yielded a response greater than the nominal 100%, as seen here.

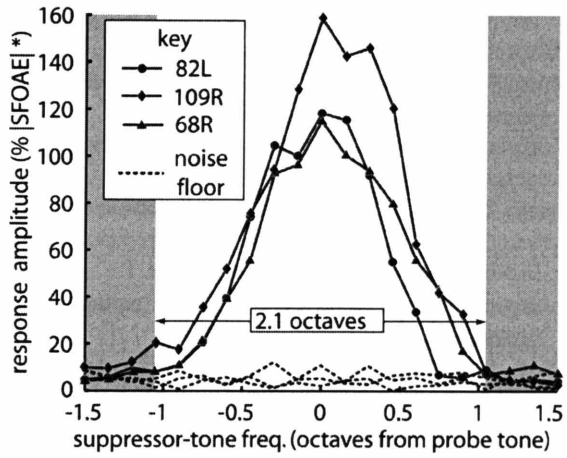


Figure 22. Bandwidth of two-tone suppression measured via the average change in SFOAE magnitude between suppressor-on and suppressor-off conditions for 60 dB SPL tone suppressors at various frequencies relative to the probe tone. 16 one-second responses were averaged for each point. Ipsilateral suppressor tones (500 ms duration) produced two-tone suppression effects (solid lines), while contralateral "suppressor tones" produced no effects (dashed lines) and were used to asses the noise floor. The edges of the gray bands demark the chosen 2.1 octave span for the spectral notch incorporated into elicitors when comparing ipsilaterally, contralaterally, and bilaterally elicited MOCR responses.

When comparing ipsilaterally, contralaterally, and bilaterally activated MOCR time-courses (results section C.), a 2.1 octave spectral notch centered at the probe-tone frequency was used for all noise-elicitors. In retrospect, since subject 109R showed some suppression at -1.05 octaves, the notch should have been extended to lower frequencies for this subject. This oversight, however, is unlikely to have much of an effect. The total level of the notched-noise elicitor was set at 60 dB SPL, therefore the elicitor would introduce much less energy at the -1.05 octave place in the cochlea than a 60 dB SPL suppressor-tone that concentrates its energy there.

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Chapter 4: Efficacy of AM Noise for Activating the Human Medial Olivocochlear Reflex

ABSTRACT

A previous study reported that amplitude modulation (AM) of an acoustic stimulus used to activate the medial olivocochlear reflex (MOCR) increased MOCR responses (Maison, Micheyl et al. 1999). We follow up on this study using stimulus frequency otoacoustic emissions (SFOAEs) to measure MOCR responses. SFOAEs were monitored in one ear while 60 dB SPL amplitude modulated (AM) wideband noise at various modulation frequencies (MFs from 0.5 Hz to 400 Hz) were presented in the opposite ear to activate the MOCR. In 3/4 subjects, AM wideband MOCR activators produced lower steady-state MOCR responses than no-AM activators. One subject showed an enhancement with AM, particularly for 100 Hz sine-wave modulations, but this enhancement was not always observed and may have been due to time-dependent variations in the measurements. The results suggest that the MOCR generally increases its steady-state response monotonically with increasing MFs and ultimately saturates at the 'no-AM' level (for wideband activators). In addition, we demonstrate that responses to square-wave AM at various MFs can be approximated by the time course of the MOCR taken from no-AM activator measurements, indicating that no major interactions between AM stimuli and the MOCR likely exist. The modulation transfer function (MTF) of the MOCR loop was quantified and compared with amplitude fluctuations in the speech envelope. Important MFs in the speech envelope (1 Hz – 11 Hz) activated the MOCR and produce both AC and DC cochlear effects. The sound levels and MFs found in conversational speech are likely to produce small DC MOCR response—conversational speech may prime the MOCR to a level where it is poised to aid speech perception if noise occurs.

ABBREVIATIONS

AC	alternating current
AM	amplitude modulation
BM	basilar membrane
CAS	contralateral acoustic stimulation
DC	direct current
EC	ear canal
FFT	Fast Fourier Transform
HF	high frequency
MD	modulation depth
MF	modulation frequency
MOC	medial olivocochlear
MOCR	medial olivocochlear reflex
MTF	modulation transfer function
OAE	otoacoustic emissions
rms	root-mean-squared
SFOAE	stimulus frequency otoacoustic emission
TEOAE	transiently evoked otoacoustic emission

I. INTRODUCTION

The medial olivocochlear reflex (MOCR) is one of several sound-activated feedback circuits that control the input to the mammalian hearing system (for a review see (Guinan 1996). Activating medial olivocochlear (MOC) fibers reduces the amplitude of basilar membrane motion in response to sound by 10-20 dB at the characteristic frequency (Murugasu and Russell 1996; Dolan, Guo et al. 1997; Cooper and Guinan 2003). Although several ideas have been put forward regarding possible roles for the MOCR in hearing, there is no consensus about its primary role. Identifying the acoustic signals that are most effective for activating the MOCR may reveal internal properties of the reflex and may aid in understanding its role in hearing.

Since the discovery of otoacoustic emissions (OAEs) (Kemp 1978), it has become common to measure MOCR effects by looking at changes induced in OAEs when the MOCR is activated by contralateral acoustic stimulation (CAS). A previous paper reported that modulating the amplitude of a wideband[33] CAS

[33] An earlier report found enhancement due to 100 Hz modulation of *tone* CAS (maximal at 37% MD) (Maison, Micheyl et al. 1997) but this enhancement was likely due to the modulation adding more frequencies to the CAS. The MOCR's response was reported to increase with CAS bandwidth (Maison, Micheyl et al. 2000).

with a 100 Hz sine-wave at 100% modulation depth (MD) enhanced MOCR responses, i.e. produced a greater reduction in transiently evoked otoacoustic emissions (TEAOEs). Although other combinations of modulation depths (MD = 25%-100%, 5 modulation depths) and frequencies (MF = 50 – 800 Hz, 9 frequencies) were tried, only the 100% MD, 100 Hz MF combination significantly (paired t, $P < 0.05$) enhanced the MOCR response over un-modulated CAS (Maison, Micheyl et al. 1999). If true, this result would be interesting because it suggests that there is a special interaction between acoustic signals modulated at 100 Hz and the MOCR reflex; such an interaction may reveal an internal 'resonance' in the reflex. One motivation for this study was to replicate the 100 Hz AM result.

A second motivation was to characterize the way AM information is carried through the MOC reflex loop. Many natural sounds that carry information, such as speech, encode that information as amplitude modulation (AM). To investigate whether the MOCR could influence the neural coding of responses to AM sounds, we quantified the ability of the MOCR to respond (i.e. to affect change in |SFOAEs|) to various rates of AM modulation in CAS.

II. METHODS

We quantified the ability of the MOCR to respond to various rates of AM modulation by measuring changes in stimulus frequency otoacoustic emissions (SFOAEs) in response to contralateral AM wideband noise.

A. Overview

A "probe-tone" was played into the ear canal in order to generate an SFOAE from within the cochlea. This SFOAE combined with the probe-tone in the ear canal to produce a compound-tone[34], **C**(t), the ear canal sound pressure at the probe-tone frequency (Figure 23). If the acoustic probe-tone stimulus is invariant, e.g. if there is no middle-ear-muscle (MEM) contraction, changes in the compound-tone can be wholly attributed to changes in the SFOAE, i.e. **ΔSFOAE**(t). Since activation of medial-olivocochlear (MOC) fibers reduces the sound-induced motion of the basilar membrane (BM) (Murugasu and Russell 1996; Dolan, Guo et al. 1997; Cooper and Guinan 2003) it is likely that MOCR inhibition of SFOAEs is caused by the reduction of BM motion[35].

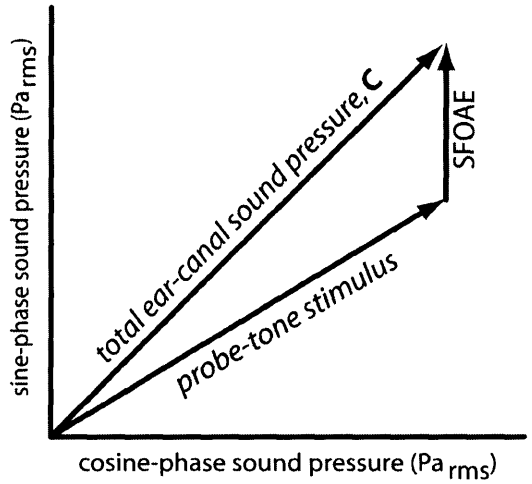

Figure 23. Vector diagram representing the summation in the ear-canal (EC) of two tonal components that differ in magnitude (length of arrows) and phase (direction of arrows). A tone stimulus (probe-tone) and the SFOAE it generates add to produce a compound-tone, C, that is measured as the EC sound pressure at the probe-tone frequency. If the probe-tone component is invariant, any change in the measured EC sound pressure reflects a change in the SFOAE magnitude and/or phase.

B. Subjects and screening

4 young adult subjects (3 female, 1 male) were tested. A larger pool of previously measured subjects ~30 was scanned to select the 4 available subjects that gave known strong SFOAE responses. This screening was done in an effort to reduce averaging time to practically feasible durations. All selected subjects had normal hearing in both ears (within 20 dB re: ANSI pure tone threshold from 250 Hz to 4 kHz). A probe-frequency and measurement ear combination that produced a large SFOAE near 1 kHz was chosen to be measured. Each measurement ear produced an SFOAE that was 100 Hz or more from any spontaneous emission with an amplitude > -10 dB.

[34] The compound-tone, **C**(t), is a complex quantity whose magnitude and/or phase can change over time, such that $\mathbf{C}(t) = |\mathbf{C}(t)| \cdot e^{i\angle \mathbf{C}(t)}$.

[35] Strong frequency dependant variations found in chapter 5 indicate that this may not be the only way in which MOCR activation can affect SFOAEs (see Chapter 5, Discussion)

C. Acoustic stimuli

To produce SFOAEs, a continuous 40 dB SPL probe-tone (900 – 1120 Hz) was presented bilaterally through two Etymotic ER10c earphones. To elicit an MOCR response, a 4 s wideband (100 Hz - 10 kHz) contralateral noise-burst (5 ms rise/fall) was presented every 8 s, (starting at 0 s) alternating in polarity with each burst. Bursts were amplitude modulated with sine-wave AM or square-wave AM (50% duty cycle, edges smoothed with 5 ms raised-cosine rise/fall ramps) at various modulation frequencies (14 – 16 frequencies between 0 and 200 Hz, subject M68R was also measured at 400 Hz, presentation order was randomized for each subject). For comparison, a measurement was also made with an unmodulated burst (i.e. a 'no-AM' condition). All bursts were engineered to have the same overall rms energy, (55 dB SPL for subject 109 and 60 dB SPL for all others). For each subject, the noise-burst level chosen did not elicit middle-ear-muscle contractions as shown by a group-delay test (details in Chapter 3, Appendix A).

D. Response analysis

Multiple (8 – 144) stimulus presentations were made (depending on SNR and subject availability) for a given modulation type and MF (or for the 'no-AM' condition) and the EC sound pressures generated in the test ear were averaged. The magnitude and phase of the average EC sound pressure at the probe-tone frequency was extracted by heterodyning (Kim, Dorn et al. 2001; Guinan, Backus et al. 2003). Finally, the *change* in EC sound pressure at the probe-tone frequency over time—due to the MOCR-mediated changes in the SFOAE over time—was calculated by vector subtraction to produce **ΔSFOAE**(t). Specifically, the pre-elicitor baseline average (mean from the shaded baseline window in Figure 23, -480 < t < -80) was vector subtracted from each time point.

1. DC analysis

To address the question of whether high-frequency amplitude modulation (HF-AM, considered to be 20 Hz and above in this study) enhances steady-state MOCR responses, a DC (long-time-average) analysis of the **ΔSFOAE**(t) was done.

Calculating individual DC values

The steady-state response at a particular MF was taken to be the magnitude of the complex average of the response taken over a 3 second time window (980 < t < 3980),

$$MOCR_{DC}(MF) = \left| \frac{\sum_{t=980ms}^{3980ms} \Delta\mathbf{SFOAE}(t, MF)}{number\ of\ time\ samples} \right| \quad (1)$$

Calculating errors in individual DC values

Measurement error came from two sources: (1) random noise (2) slowly varying 'baseline shifts'[36]. DC analysis (averaging responses across time) was susceptible to both sources and was particularly susceptible to baseline drift.

To quantify the total error associated with time-averaged (i.e. steady-state or DC) MOCR responses we estimated the error contributions from random noise and baseline shift separately and then added them to produce a total error estimate and the error bars in Figure 25 and Figure 26.

In order to estimate errors from random noise, a bootstrap technique was used[37]. For the bootstrap, the 'N' vectors averaged while computing the DC MOCR effect (e.g. Eq. 1), were pooled. Statistically similar data sets were then generated by taking N samples at random with replacement from the pool. 1000 such sets were generated. These sets were used to compute 1000 new estimates of the mean and their standard deviation was used as the estimate of the error caused by random noise. This error was added to upper and lower error bars.

To estimate the error caused by baseline shifts, two 400 ms windows—where the response was expected to be 0—were compared: (1) an early window (-480 < t < -80) ms and (2) a late window (7080 < t < 7480)[38]. The complex average in each window was computed and then the vector difference between those averages was computed. The

[36] Slow baseline shifts may be related to (a) changes in the fit of the ER10c earphones in the ECs or (b) the slow MOCR time constant, τ_{slow} = 10's of seconds, discussed in Chapter 3.

[37] The error of the magnitude estimate of a 'mean vector' due to random noise depends upon its constituent magnitudes and phases and cannot be calculated in the same way the errors of real-valued numbers. The bootstrap estimate of the error had the advantage that it required no assumptions about the underlying magnitude and phase distributions and how they were coupled.

[38] The 'baseline' used to calculate **ΔSFOAE**(t) was always the early window.

magnitude of the difference was the amount the baseline shifted during a measurement and was used as the 'error due to baseline shift.' Although it was possible to tell in which direction the baseline shifted, the error was not used to correct for baseline shifts as there was no proof that such shifts were monotonic or uniform. Instead the error was added to upper and lower error bars to represent a worst case estimate of how much baseline shifts may change a reported MOCR response.

2. AC analysis

To approximate the MOCR's modulation transfer function (shown in Figure 27) and thereby quantify the fraction of AM (at a given frequency) that is carried through the reflex loop, an AC analysis of **ΔSFOAE**(t) responses to AM CAS was performed as follows:

(1) The time window between 980 ms and 4000 ms was trimmed to contain an integer number of modulation cycles. The window was used to select a subset of the **ΔSFOAE**(t) response, **ΔSFOAE**(w), All other data points were discarded.
(2) The average (DC component) of **ΔSFOAE**(w) was subtracted from each time point in **ΔSFOAE**(w).
(3) An FFT was taken to extract the first 4 harmonics of the modulation frequency.
(4) The total peak-to-peak amplitude generated by these harmonics was normalized by the DC response amplitude (magnitude of the average between 980 ms < t < 3980 ms) from a 'no-AM' measurement made in the same ear and at the same overall level but at a different time[39].

Measurement error was not calculated during AC analysis for each individual because unlike the DC results, we do not emphasize individual AC responses, instead the average AC response across individuals and the SD between individuals is reported.

3. Normalization

Measurement data are presented in 3 formats: raw change in EC sound pressure (μPa_{rms} and dB SPL), percent change in SFOAE amplitude (% |SFOAE|), and amount of AC vs. DC components in the response (as a fraction or in % modulation depth). The last 2 formats involved normalization.

Normalization by |SFOAE|

Since 3 of the 4 ears measured here had previously characterized contralateral MOCR time-courses (F109R, M68R, F82L in Chapter 1), the same normalization was repeated here to allow straightforward comparisons to the prior work. For this normalization, a two-tone suppression measurement using a 400 ms suppressor-tone placed 110 Hz below the probe-tone frequency was used to suppress the SFOAE. The SFOAE was presumed to be completely suppressed and the average change in ear-canal (EC) sound pressure was taken as an estimate of the SFOAE. This estimate was used to normalize the MOCR responses such that response magnitudes are presented in terms of the percent of |SFOAE| inhibited (details see Chapter 1, Appendix B).

Normalization of the AC components of AM responses by the DC component of no-AM responses

In order to compare the relative contributions of AC and DC components of AM responses for various MFs, we normalized the AC components of the response elicited by AM noise by the DC response elicited by a non-modulated noise presented at the same overall rms level (55 or 60 dB SPL) to the same ear, as described in step (4) of the AC analysis procedure.

[39] The modulation depth in Figure 5 exceeded 100% when amplitude of combined AC components exceeded the amplitude of the DC component from the 'no-AM' measurement used for normalization. This could be due to time-dependent variations discussed in Results A.

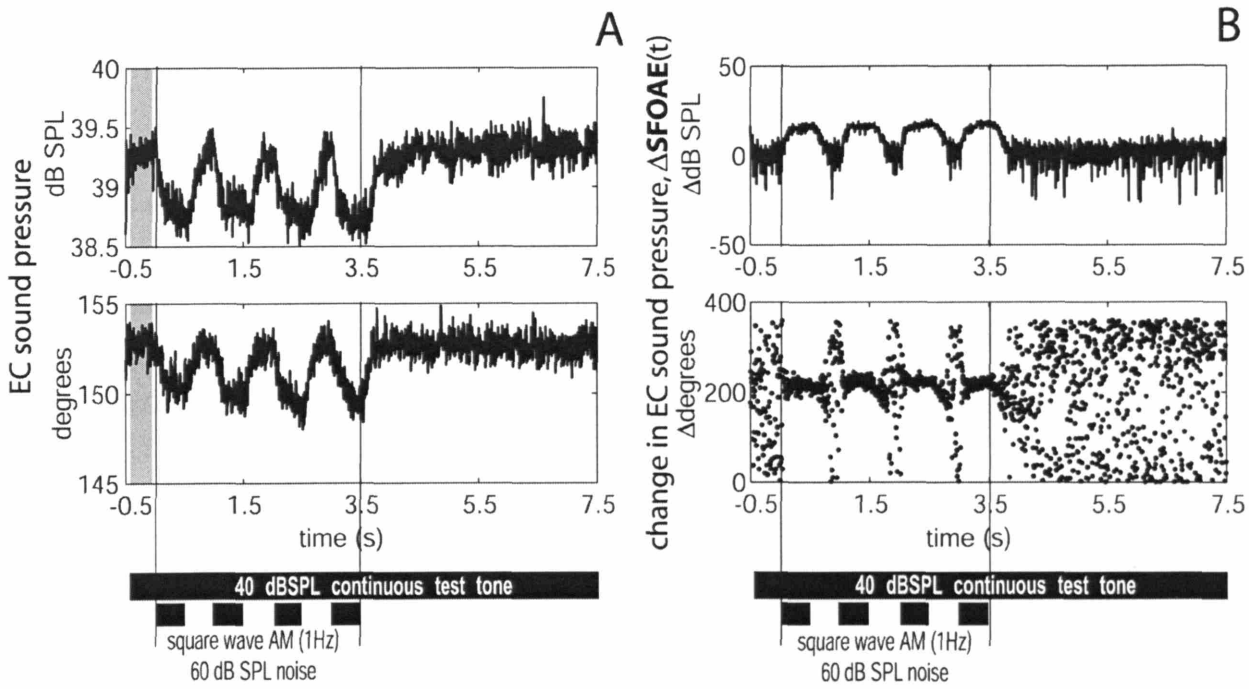

Figure 24. Panel A show the amplitude and phase of the ear canal sound pressure at the probe-tone frequency (1120 Hz) during an 8 s measurement (subject F109R, right ear). A contralateral (left ear) 60 dB SPL wideband noise elicitor with square wave (5ms rise/fall) AM at a modulation frequency of 1Hz was presented between 0 s < t < 4.0 s. Panel B shows the change in ear canal sound pressure calculated by vectorially subtracting the mean baseline magnitude and phase (from the shaded window at left, -480 ms < t < -80 ms) from each time point.

III. RESULTS

Figure 24 shows normalized MOCR responses for the no-AM condition and for all AM frequencies measured for subject F109R. All subjects produced qualitatively similar results.

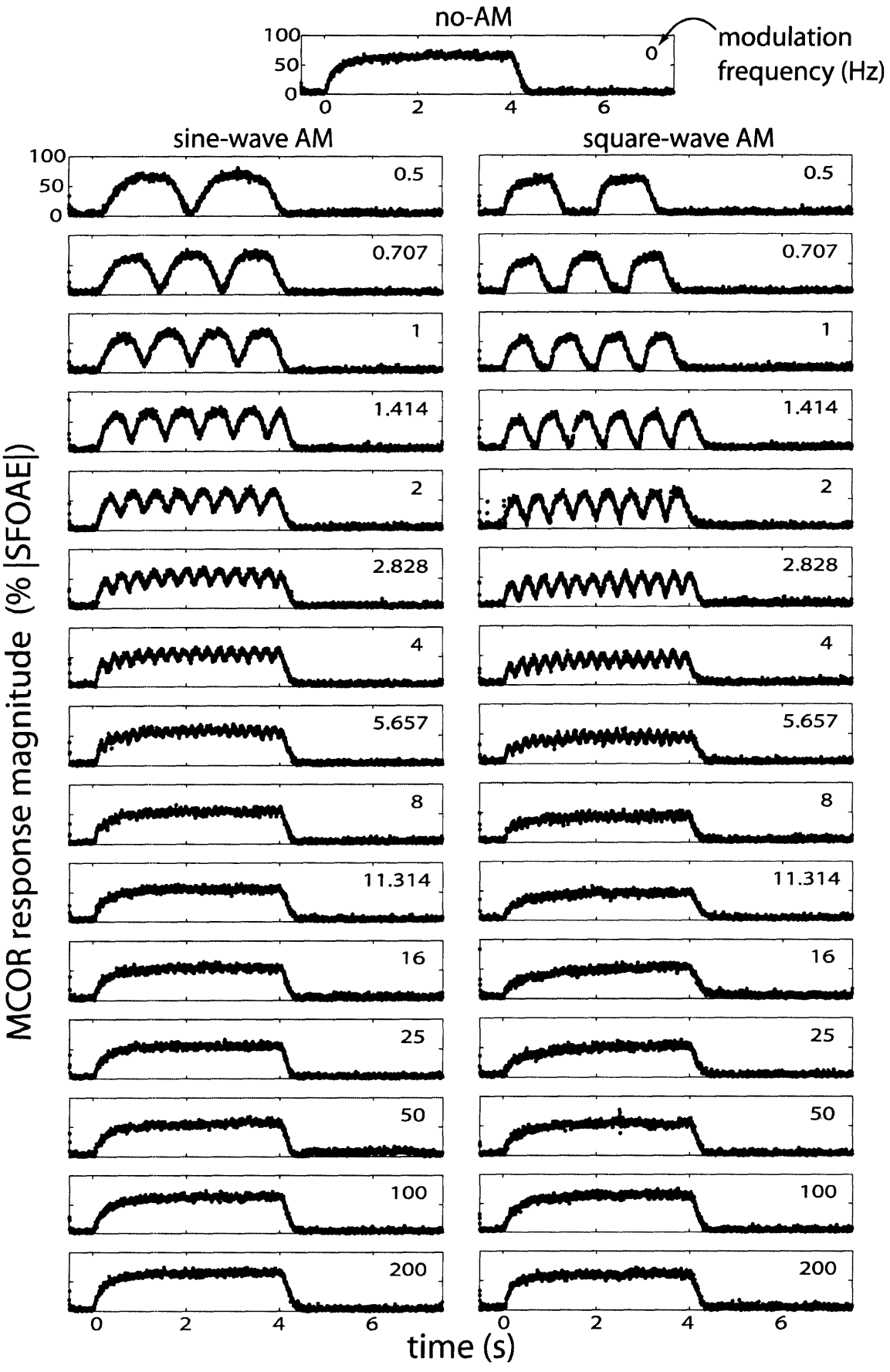
no-AM
100
50
0
0
0
2
4
6
modulation
frequency (Hz)
sine-wave AM
square-wave AM
MCOR response magnitude (% |SFOAE|)
0.5
0.707
1
1.414
2
2.828
4
5.657
8
11.314
16
25
50
100
200
time (s)

Figure 25. MOCR responses to sine-wave (left panels) and square-wave (right panels) AM contralateral wideband noise bursts (4 s duration, 60 dB SPL, 100% MD) at various frequencies (listed in Hz) for subject F109R. Measurements were normalized by an estimate of the SFOAE amplitude from a standard two-tone suppression measurement. Responses are reported as the percent change in |SFOAE|. Top center panel shows a similar measurement but with no modulation (0 Hz). AM noise bursts started at 0 s and were a maximum of 4 seconds in duration. When modulated, noise bursts contained the largest integer number of modulation cycles spanning less than 4 seconds. Each measurement was composed of 80, 8 s averages.

A. High frequency (20 Hz – 200 Hz) amplitude modulation of the MOCR activator decreased the steady-state MOCR response in 3/4 subjects

The steady-state portions of MOCR responses to high-frequency (HF) AM activators were analyzed to test whether HF-AM increased MOCR steady-state responses. For the test, both square-wave and sine-wave AM (MD = 100%) at MFs from 20 and 400 Hz were presented. Three of 4 subjects did not show enhancement from HF-AM. Subject M68R, however, did show an apparent enhancement at 100, 200, and 400 Hz for sine-wave modulation and possibly at 400 Hz for square-wave modulation. However, only the 100 Hz sine-wave AM enhancement was statistically significant enhancement at the $P < 0.05$ level (Figure 26).

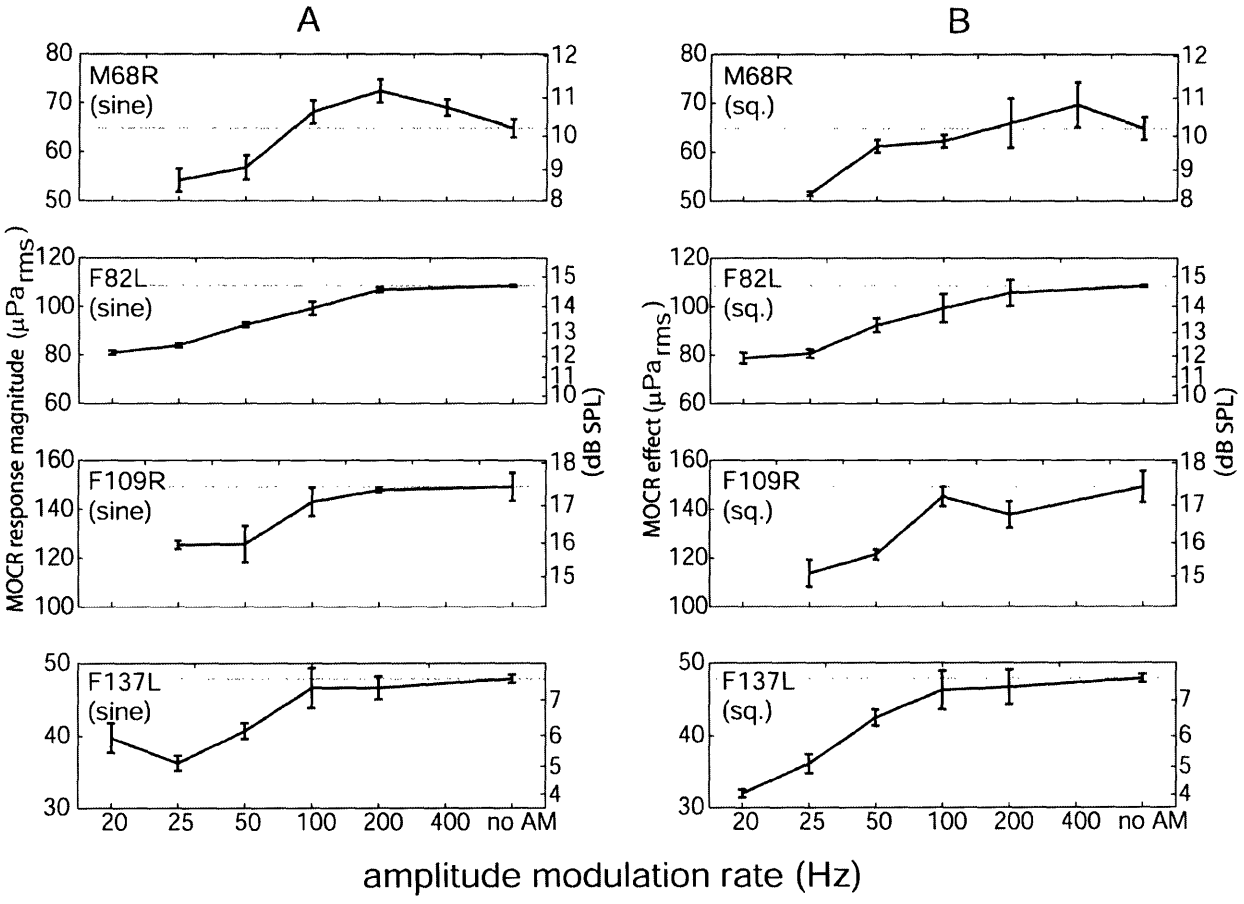

Figure 26. Average steady-state change in SFOAEs induced by MOCR activation with CAS having either sine-wave (Panel A) or square-wave (Panel B) AM at various frequencies and a 'no-AM' condition (average no-AM level is also represented with a dotted line for comparison). AM modulation failed to enhance the MOCR induced

responses over no-AM in 3/4 subjects, but M68R did show significant (P<0.05) enhancement at 100 Hz for sine-wave AM. Values were computed by time-averaging respective DSFOAE(t)'s across a 3 s window (980 < t < 3980) during which the responses were essentially constant (~3 time constants of the initial buildup having elapsed prior to the start of the averaging window). Error bars are 1 SE + observed drift (see Methods). The total rms acoustic energy in all elicitors was kept constant. Multiple (20 - 36) presentations were averaged per point.

B. Repeatability and time-dependent variations in the measurements

Individual measurement groups (a series of measurements made at a number of MFs) displayed time-dependent variations as a lack of repeatability (Figure 27).

The colored lines in Figure 27 represent individual measurement groups in the sense that the measurements forming each colored line were acquired during the same data gathering 'measurement group'. However, the 4 or 5 HF AM frequencies shown in Figure 27 were only a subset of the frequencies acquired (a measurement group consisted of 16 AM frequencies for M68R and 15 for F82L). Since the presentation order of all AM frequencies done in a group was randomized, there could be delays in excess of a minute between the presentations of different modulation rates (i.e. adjacent points on the colored curves in Figure 27 may have been measured a minute or more apart). Such delays allowed time-dependent variations to accrue.

Three measurement groups in Figure 27, Panel A have been emphasized (in bold) because the measurements that produced these measurement groups were made with consecutive (magenta) or nearly consecutive presentations thereby reducing time-dependent variations. The emphasized curves for M68R do not show significant enhancement for AM over no-AM conditions. Instead they show a trend more like the prevailing trend from the 3 other subjects, a monotonically increasing response with increasing AM frequency.

The above analysis suggests that the observed enhancement of M68R's response to AM noise in Figure 26 could be a consequence of randomized presentation order combined with time-dependent variations in the responses (see Discussion).

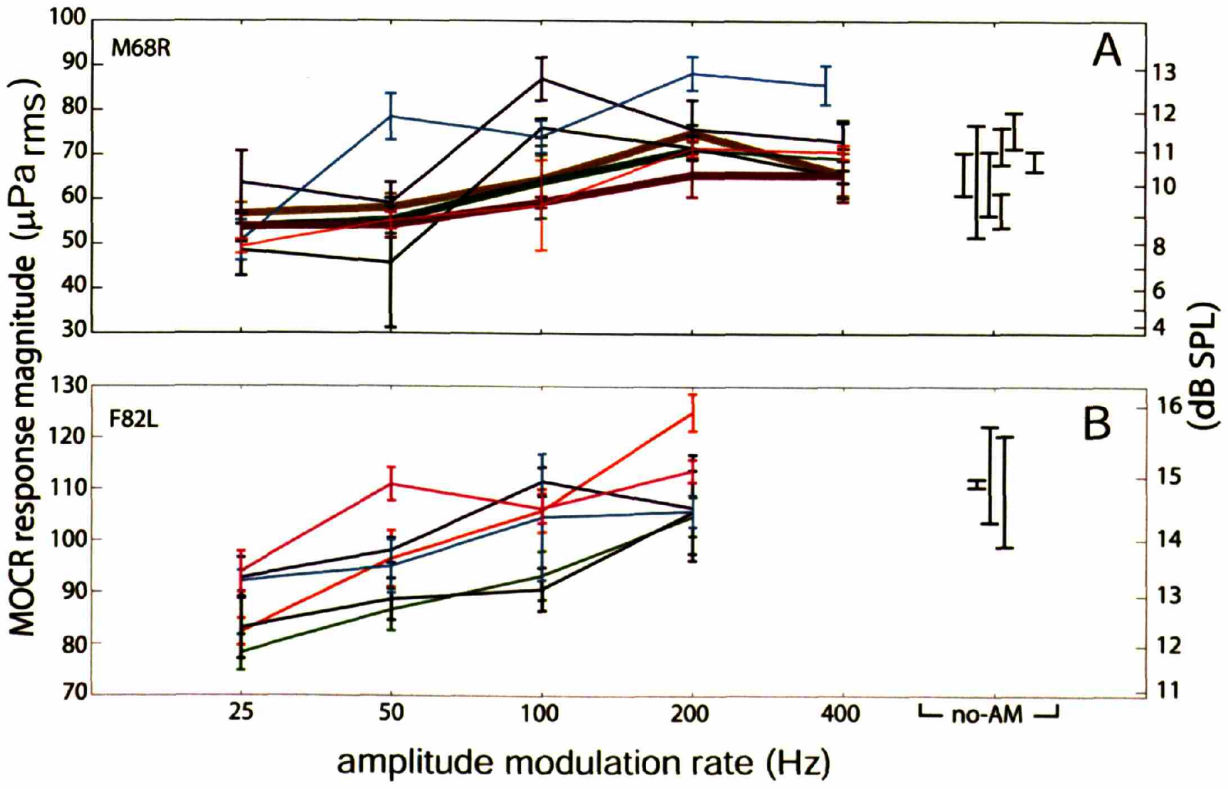

Figure 27. Individual measurement groups (colored lines) showing the magnitude of MOCR responses evoked with HF sine-wave AM elicitors at various frequencies for 2 subjects (Panels A, B). Measurement groups where measurements were more closely spaced in time (thicker lines in Panel A) did not show an increased response to AM noise elicitors for subject M68R suggesting that the increase reported in the average may be due to time-dependent variations in the measurements.

C. The modulation transfer function (MTF) of the MOCR

MOCR activation using wideband CAS with 100% AM at various frequencies was used to determine the modulation transfer function (MTF) of the MOCR.

Figure 28 shows MTFs for all 4 subjects measured using either square-wave or sine-wave AM. The ability of the MOCR to follow AM decreased with increasing AM frequency as would be expected for a system with time-constants of ~300 ms (see Chapter 3). At 2 Hz AM, ~50% of the modulation was carried through the reflex. At 10 Hz ~10% of the AM was carried through the reflex.

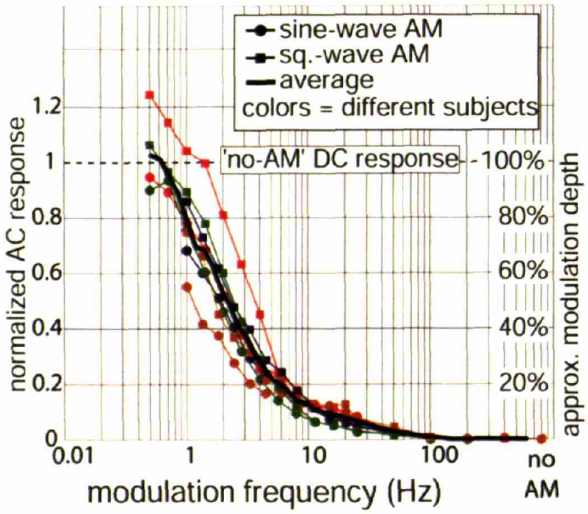

Figure 28. Modulation transfer function of the MOCR shows the fraction of AM modulation at different frequencies that were carried though the reflex loop. The MOCR's passed > 80% of AM below 1 Hz and passed < 10% of AM above 10 Hz. The values were computed by normalizing the average AC amplitude at a given modulation frequency by the amplitude of the average DC response taken from 'no-AM' measurements. Four colors represent 4 subjects (red = M68R, blue = F82L, green = F109R, rust = F137L),

D. MOCR responses to AM wideband noise can be approximated by the MOCR time-course

The MOCR's response to unmodulated wideband noise bursts was sufficient to approximate the bulk of the MOCR's response to square-wave AM elicitors (MFs between 0.5 and 50 Hz were examined[40]) for subject F109R (Figure 29). To make the approximation (red curves), subject F109R's time-course characterization from Chapter 3 was used. Approximations were made by applying onset and decay curvatures and onset and offset delays determined in Chapter 3 (see Chapter 3, Appendix C2) to the off-on or on-off CAS transitions respectively. A constant (value = 55/47) was applied equally to all MFs to account for differences in the steady-state levels between the previous characterization and the measurements made here.

[40] MFs at and above 100 Hz could not be used because the rising rates of the first 10 ms was not well determined by the previous characterization (10 ms was represented by only two samples points).

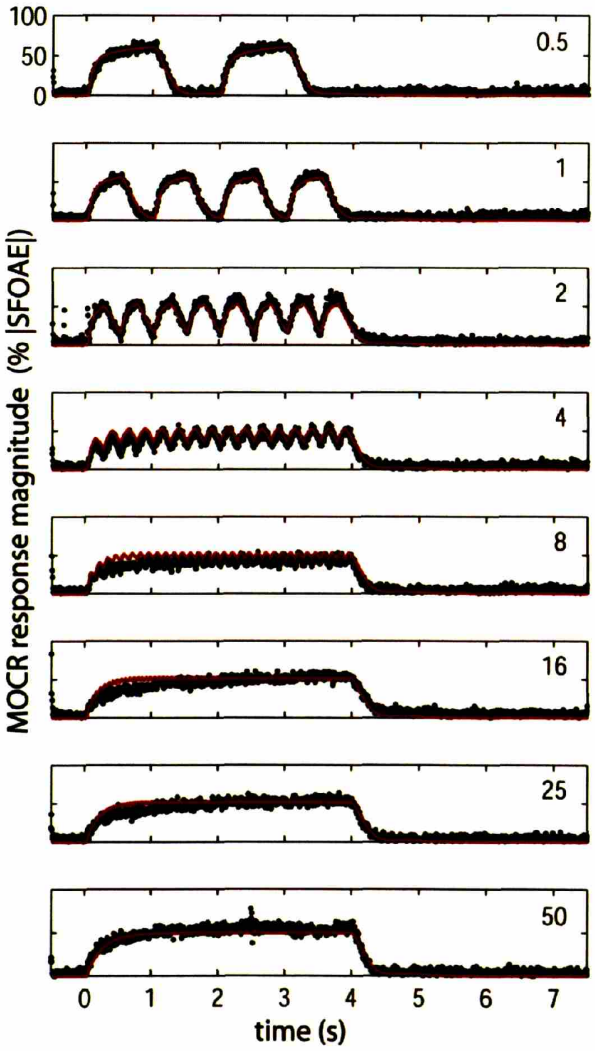

Figure 29. Approximated MOCR responses to square-wave AM based on the time-course characterization made for this subject (F109R) from chapter 1 (red curves) superimposed on actual measured MOCR responses to 50 dB SPL square-wave AM CAS at various frequencies (enumerated in each panel in Hz). The MOCR time-course characterization was sufficient to approximate the MOCR's response to square-wave AM elicitors although minor differences in the rising portions were observed. Approximations (red curves) were generated by applying previously determined rise and fall rates and delays to each off-on, or on-off, transition in the AM CAS and are based on the idea that the MOCR is linear with regards to these inputs.

Both AC and DC (steady-state) components of the responses were well approximated, suggesting that there were no major non-linear interactions between the AM elicitors tested and the MOCR reflex. Some departures from approximations were observed, particularly in the rising portions of the 8 Hz, 16 Hz and 25 Hz MFs; but it was not determined whether these constituted real differences, or if they were due to measurement variability, or time-dependent variation.

IV. DISCUSSION

A. Does AM enhance efferent elicitor efficacy?

Our results do not generally show an enhanced efficacy of AM noise relative to unmodulated noise in eliciting steady-state MOCR responses (Figures 26, 27). This result is different from previous reports (Maison, Micheyl et al. 1997; Maison, Micheyl et al. 1998; Maison, Micheyl et al. 1999). Although we did observe an enhanced average response from HF AM elicitors in one subject, there was a question as to whether this observation constituted a true effect or whether it was due to time-dependent variations in the responses. In general, adding HF AM did not enhance MOCR effects on SFOAEs.

Although a large enhancement was previously found to be produced by AM tones relative to un-modulated tones (Maison, Micheyl et al. 1999), the increase was likely caused by frequency summation. Pure tones are weak efferent elicitors (Guinan, Backus et al. 2003), but an AM tone contains energy at additional frequencies (the tone frequency +/- the modulation frequency) and since MOCR response increases with increasing elicitor bandwidth (Norman & Thornton, 1993; Micheyl et al., 1999; Maison et al., 2000; Lilaonitkul et al., 2002; Velenovsky & Glattke, 2002) an increased response to AM tones over tones alone is to be expected.

The previously reported results using AM wideband noise elicitors and TEOAEs found a statistically-significant ($P<0.05$) enhancement of steady-state efferent effects (greater TEOAE suppression) for AM elicitors when the MF was 100 Hz and MD was 100% (Maison, Micheyl et al. 1999). They also reporteded a decreased response to elicitors with an AM rate of 50 Hz (Maison et al., 1999). Our results suggest that responses generally increase with increasing MF and ultimately saturate at the no-AM response level (consistent with the 50 Hz finding but not the 100 Hz finding). Although 1 subject, M68R, did show significant enhancement ($P< 0.05$) for 100

Hz AM, it was not significant in the sense that the result was not repeatable. Closer inspection indicated that the enhancement could have been due to time-dependent variations that were exacerbated by our decision to randomize the presentations of all MFs within a measurement group and to measure unmodulated responses in separate runs. Whether, under some circumstances for some subjects, HF AM (e.g. 100 Hz) can enhance MOCR responses is still not known. To settle this question, experiments on more subjects need to be done in a manner that minimizes time-dependent variations (i.e. unmodulated responses must be measured before and after each AM measurement).

Although the question of whether AM enhancement may exist under some circumstances is not settled, the demonstration that an MOCR time-course derived from an unmodulated elicitor can approximate the DC levels evoked by AM modulated elicitors in (Figure 29) supports the idea that

"MOCR steady-state responses increase monotonically with increasing MFs and saturate at the 'no-AM' level,"

because if the approximation were exact true, it would indicate that the MOCR behaved linearly with respect to these AM stimuli, and would produce that result exactly.

B. A comment regarding the modulation transfer function of individual MOC neurons

Single MOC neurons in guinea pigs have been shown to have a peak in their modulation transfer functions (MTF) at ~100 Hz measured with AM tones (Gummer, Yates et al. 1988) and this might be thought to lead to an increased output of the MOCR for 100 Hz AM stimuli. However, any HF-AM firing pattern is expected to be low-pass filtered by the peripheral cellular machinery responsible for effecting changes in the cochlea[41], so it is the average rate (not the MD) of MOC neurons that probably determines the ultimate steady-state MOCR response level in the cochlea. Grummer et al. (1988) do not report on whether there was a concomitant increase in *average* firing rate at 100 Hz for these neurons—an increased MD within the MOC firing pattern does not necessarily mean increased average rate because the MD can increase by having *fewer* spikes in 'off' half cycles. Increases in the AC output of MOC neurons at 100 Hz does not necessarily translate into an increased DC response for the reflex as a whole. We found the MOCR steady-state responses typically decreased for 100 Hz sine-wave AM activators.

C. Implications for efferent function and speech

The MTF describes how faithfully modulation can be carried through the reflex loop, and can be useful when identifying which sounds the reflex may able to operate on.

Our MTF results show that the frequency following ability of the MOCR is not well adapted to make within-cycle changes at the modulation frequencies that contain the most information in speech[42] (Figure 30). The most important MFs for speech are between 1-11 Hz (N. Kanedera, Arai et al. 1997), and at those frequencies the MOCR produces AC changes of 10-70% of its steady-state change. The MOCR's AC response has a high-frequency cutoff at ~1 Hz and a slow roll-off across the most important MFs in speech. Thus, the MOCR is not likely to be operating on the information bearing part of the speech envelope.

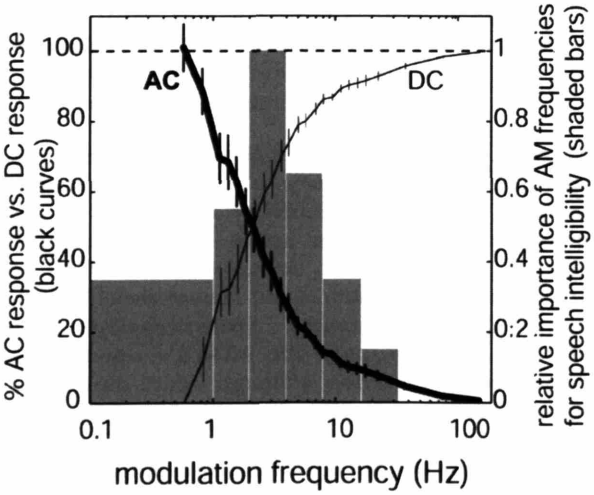

Figure 30. Ability of MOCR to follow modulation at various AM frequencies (bold black curve, error bars = 1 SD) superimposed on the relative importance of various modulation frequencies (in bands) found in the speech envelope for intelligibility (Kanedera et al.

[41] Our MTFs show virtually no AC components remain at 100 Hz. This is expected because the MOCR has relatively slow onset and decay rates (τ=~330 ms, τ=~150 respectively). These rates may be governed by cellular processes involving outer hair cells (see Chapter 3, Discussion).

[42] If used as a filter, the MOCR would seriously degrade speech intelligibility.

1997). The MOCR is not well-adapted to 'follow' the information carrying portion of speech, however, the MOCR can produce both AC and DC responses to modulation rates found in speech.

The response of the MOCR, however, may play an important role in increasing the intelligibility of speech in noisy backgrounds by suppressing auditory-nerve responses to background noise (Kawase, Delgutte et al. 1993; Micheyl and Collet 1996; Giraud, Garnier et al. 1997; Hienz, Stiles et al. 1998). For this strategy to work, the MOCR must be active during speech, but it need not 'follow' the speech envelope. Our results show that the MOCR produces a mixture of AC and DC responses in the cochlea for speech-like MFs. It is interesting to note that a steady-state DC response was always produced over the 1-11 Hz AM range[43] (Figures 28, 30) and that this DC response was produced using normal conversational sound levels (the levels used in this study, 50 and 60 dB SPL, are considered to be within the normal conversational range). In our study, the MOCR was *always* active for 1-11 Hz AM, however, our CAS did not have the spectral content of speech; thus, it is not possible to conclude that the MOCR is *always* active while one listens to speech[44], but it seems likely. In any event, the modulation rates found in speech can activate the MOCR thereby producing both AC and DC cochlear effects. It is possible that the sound levels and modulation rates in speech 'prime' the MOCR to an activity level that is poised to react to noise in a way that preserves the informational speech signal.

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[43] There is a trade off that occurs in this 1-10 Hz modulation region—'AC information' is converted to 'DC information'. We speculate that the 'DC information' may be important to the function of the MOCR.

[44] Since the MOCR is known to integrate across frequency (Maison, Micheyl et al. 2000), it is likely that the MOCR response would be less for speech-shaped noise (perhaps at or near the 'always on' threshold).

Chapter 5: The Distribution of Medial Olivocochlear Reflex Strengths across Normal-Hearing Individuals

ABSTRACT

In order to determine the distribution of medial olivocochlear reflex (MOCR) strengths across a normal-hearing population, stimulus-frequency otoacoustic emissions (SFOAEs) within 10% of 1 kHz were monitored while the medial olivocochlear reflex (MOCR) was activated with 60 dB SPL wideband contralateral acoustic stimulation (CAS). MOCR effects could be measured in 25/25 subjects but not all SFOAE frequencies produced measurable effects. 'Single-frequency MOCR normalized effects' (defined as the percent change in an SFOAE's amplitude due to MOCR activation) were found to vary rapidly across frequency—measurements made as little as 40 Hz apart in the same ear produced significantly different results—and across time—measurements made minutes apart could produce significantly different results. Averaging several single-frequency measures (spanning 200 Hz) from the same subject was able to reduce the frequency and time-dependent variations enough to produce correlated ($R = 0.47$, $P = 0.022$) measures of 'regional MOCR strength' for that subject. The distribution of these regional MOCR strengths near 1 kHz across our normal-hearing subject pool was reasonably approximated by a normal distribution with mean ~30% and SD=10%.

ABBREVIATIONS

BM	basilar membrane
CAPD	central auditory processing disorder
CAS	contralateral acoustic stimulation
CF	characteristic frequency (a cochlear location)
DPOAE	distortion-product otoacoustic emission
EC	ear canal
f	frequency
FFT	Fast Fourier Transform
KS	Kolgormorov-Smirnov
MEM	middle ear muscle
MEMR	middle ear muscle reflex
MOC	medial olivocochlear
MOCR	medial olivocochlear reflex
OCB	olivocochlear bundle
OHC	outer hair cell
P	significance probability ($P < 0.05$ is considered statistically significant)
R	correlation coefficient
SE	standard error of the mean
SD	standard deviation
SL	sensation level
SNR	signal to noise ratio
SFOAE	stimulus-frequency otoacoustic emission
ΔSFOAE(t)	time varying change in complex stimulus frequency emission (calculated)
TEOAE	transiently-evoked otoacoustic emission

I. INTRODUCTION

The medial olivocochlear reflex (MOCR) is one of several sound-activated feedback circuits that control the input to the mammalian hearing system (for a review see (Guinan 1996). Activating medial olivocochlear (MOC) fibers reduces the amplitude of basilar membrane motion in response to sound by 10-20 dB at the characteristic frequency (CF) (Murugasu and Russell 1996; Dolan, Guo et al. 1997; Cooper and Guinan 2003). Although there are considerable data on the cochlear effects of activating the MOCR in humans (Collet, Veuillet et al. 1994; Buki, Wit et al. 2000; Kim, Dorn et al. 2001), the variation of reflex strengths across normal-hearing individuals has only been studied by De Ceulaer et al. (2001).

Establishing the range and variation of MOCR strengths (and how best to measure them) could have both scientific and clinical impact. Scientifically, such knowledge may help identify people with abnormal MOCR function. Measuring how these abnormal subjects perform in various psychoacoustic tests, such as speech detection in noise, could lead to insight into the role(s) the MOCR plays in hearing (Bar-Haim, Henkin et al. 2004). Clinically, knowing the range and variation of MOCR strengths in the normal-hearing population may prove useful for screening normal-hearing individuals for susceptibility to acoustic trauma, before any damage takes place because a stronger reflex may provide greater protection (Maison and Liberman 2000).

Although differences in MOCR effects across subjects have been observed using both transiently

evoked otoacoustic emissions (TEOAES) (Micheyl, Morlet et al. 1995; Micheyl and Collet 1996) and distortion product otoacoustic emissions (DPOAES) (Kim, Dorn et al. 2001), these studies were not designed to quantify inter-subject variations and insight is limited when these data are used to address variability. One study using TEOAEs did provide normative data on MOCR strength (De Ceulaer, Yperman et al. 2001) but neither this study nor those mentioned previously consider how measured *effects* relate to reflex *strength,* nor do they address how much of the observed variation across subjects was due to measurement variability within a subject. In other words, "how much of the observed inter-subject variation is real and how much is a consequence of the measurement method?" In addition, these studies have methodological difficulties. For TEOAE-based studies, it has been shown that the 'click' stimulus used to elicit a TEOAE can activate the MOCR itself (Guinan, Backus et al. 2003) making quantifying the baseline TEOAE level (the level without MOCR activation) difficult. For DPOAE-based studies, DPOAEs are a mixture of two emission components (Shera and Guinan 1999), and DPOAE-based methods must contend with untangling the MOCR strength from this potentially complicated mixture. For these reasons it is still not known how much variation there is in MOCR strength across the normal human population.

We used stimulus-frequency otoacoustic emissions (SFOAEs) to quantify the inter-subject variations of MOCR reflex strength in 25 normal-hearing individuals. One disadvantage of using SFOAEs is that SFOAE amplitudes vary widely across frequencies and ears making inter-subject comparisons of raw SFOAE-based measurements difficult, and necessitating normalization. However, the advantage of an SFOAE-based method is that the single low level tone stimulus does not itself activate the MOCR (Guinan, Backus et al. 2003), and it does not contain multiple frequencies that could interact within the cochlea. Thus, SFOAEs lead to a more straight forward interpretation of cochlear effects than previous methods.

The use of SFOAEs provided another advantage over other OAEs, namely since SFOAEs are measured at a single frequency, they are the most frequency-specific OAE-based measure. Initially, we did not expect to find subject-specific frequency dependence of MOCR reflex measures because individual MOC efferent fibers have been reported to span large (10^{ths} of octaves to a full octave) cochlear regions (Liberman and Brown 1986), suggesting that activating the MOCR with wideband noise would reduce OAEs *uniformly* or with only slow variation across frequency. In other words, we expected that a single single-frequency MOCR effect, once normalized, would provide a good estimate of the regional reflex strength (by 'regional' we mean the average strength in a region within 10-20% of a characteristic frequency place in the cochlea). The use of SFOAEs revealed that these expectations were not met and allowed us to probe the issue. Fortunately we were able to overcome these difficulties by averaging across frequency and time to provide a good measure of reflex strength.

II. METHODS

A. Overview

A "probe-tone" was played into the measurement ear's ear canal (EC) in order to generate an SFOAE from within the cochlea. This SFOAE combined with the probe-tone in the ear canal to produce a compound-tone[45], $\mathbf{C}(t)$, i.e. the ear canal sound pressure at the probe-tone frequency (Figure 31). If the acoustic probe-tone stimulus and middle-ear transmission function are invariant, e.g. if there is no middle-ear-muscle (MEM) contraction (see Chapter 3, Appendix A), changes in the compound-tone can be wholly attributed to changes in the SFOAE, $\Delta\mathbf{SFOAE}(t)$. Since activation of medial-olivocochlear (MOC) fibers reduces the sound-induced motion of the basilar membrane (BM) (Murugasu and Russell 1996; Dolan, Guo et al. 1997; Cooper and Guinan 2003) it is likely that MOCR inhibition of SFOAEs is caused at least in part by the reduction of BM motion (for a discussion of different mechanisms by which MOCR activation may change SFOAEs see Discussion A).

[45] The compound-tone, $\mathbf{C}(t)$, is a complex quantity whose magnitude and/or phase can change over time, such that $\mathbf{C}(t) = |\mathbf{C}(t)| \cdot e^{i\angle\mathbf{C}(t)}$.

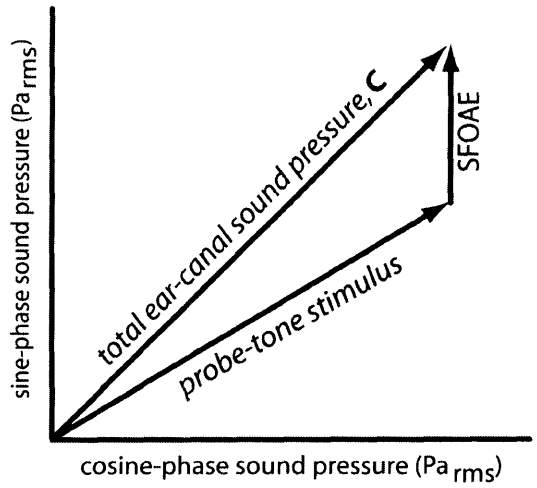

Figure 31. Vector diagram representing the summation in the ear-canal (EC) of two tonal components that differ in magnitude (length of arrows) and phase (direction of arrows). A tone stimulus (probe-tone) and the SFOAE it generates add to produce a compound-tone, C, that is measured as the EC sound pressure at the probe-tone frequency. If the probe-tone component is invariant, any change in the measured EC sound pressure reflects a change in the SFOAE magnitude and/or phase.

An SFOAE's amplitude and phase was monitored via a heterodyne technique (Kim, Dorn et al. 2001; Guinan, Backus et al. 2003) over a time period during which a contralateral wide-band noise burst was presented to activate the MOCR. The change in EC sound pressure (magnitude and phase) at the probe-tone frequency due to MOCR activation was used to quantify the MOCR *raw effect* (see Chapter 3 for details).

Since MOCR *raw effects* are measured as changes in EC sound pressure and since SFOAEs are simultaneous with, and at the same frequency as, probe-tones, it is not possible to measure SFOAEs alone—only changes in the emission can be measured. Consequently, a two-tone suppression measurement was used to estimate the native amplitude of the SFOAE (see Methods E.). This was necessary to account for variations in native SFOAE amplitudes across ears and frequencies, and allowed us to translate MOCR *raw effects* on SFOAEs (measured as EC sound pressure changes) into MOCR *normalized effects* expressed as the *percent* of the |SFOAE| altered by MOCR activation. The normalization enabled us to compare across ears and/or frequencies.

B. Subjects and screening

Twenty-five normal-hearing adult subjects (18 female, 7 male), aged 19 to 54 years (mean age = 26 years, SD = 8 years) participated in the study. The only requirement for participation was 'normal-hearing' in both ears. A two-interval forced choice audiogram using 1/3 octave band noise bursts centered at 250Hz, 500Hz, 1kHz, 2kHz, and 4kHz was used to test whether subjects had normal hearing in both ears (within 20 dB re: ANSI pure tone thresholds). All subjects who presented normal-hearing were included. 2 Subjects who didn't pass the hearing test were omitted.

Measurements of spontaneous emissions in quiet showed that no measurement ear had spontaneous emissions > -10 dB SPL within 50 Hz of any probe-tone. A middle ear muscle reflex (MEMR) group delay test (see Chapter 3 Appendix A for details) was used to insure that MOCR effects dominated the measured changes in the ear-canal sound pressure.

C. Measurement details and stimuli

Subjects were comfortably seated in a sound-absorbing chamber and fitted with 2 Etymotic Research ER10c earphones (each equipped with 2 sound sources and a microphone) for ~30 minute measuring sessions. Sessions were interleaved with ~15 minute breaks.

One ear, the 'test ear', from each subject was chosen at random (coin flip) to be measured, except for subject M166 who was measured in both ears[46] (13 left ears, 13 right ears). Each measurement ear was initially measured with low resolution (4 averages) at 11 probe-tone frequencies from 900 - 1100 Hz (20 Hz steps). Two of these probe-tone frequencies: 1 kHz and a frequency between 0.90 and 1.11 kHz that produced a comparatively large SFOAE[47] were chosen for high resolution measurements (8-284 averages depending on measurement SNR, mean = 102, SD = 50).

A measurement was composed of an average of trials[48] (4 - 284), each lasting 8 seconds. For each trial, a continuous 40 dB SPL probe-tone was presented bilaterally through one sound source from each ER10c

[46] Subject M166, however, was only measured at 1 kHz in each ear, and did not have all the data of the other subjects.
[47] Usually, the largest SFOAE was selected. If the largest SFOAE was at or within 21 Hz of 1 kHz, 900 Hz or 1100 Hz was chosen at random to be the probe-frequency.
[48] Only trials that showed less than 10 dB SPL basline shift, as measured by the magnitude of the difference between the means from region 6 and region 0.

earphone. To elicit an MOCR response, a 4 second contralateral (re: the 'test ear') wideband (100 Hz - 10 kHz flat ear-canal spectrum) noise-burst (5 ms rise/fall) was presented through the second source of the contralateral earphone every 8 seconds, alternating polarity with each burst. To estimate the amplitude of the SFOAE being measured, a two-tone suppression measurement was incorporated by adding two 400 ms, 60 dB SPL ipsilateral tone bursts at a frequency 110 Hz below the probe-tone frequency (played through the second sound source in the ipsilateral earphone). One suppressor burst was played during MOCR activation, and one was played alone (Figure 32).

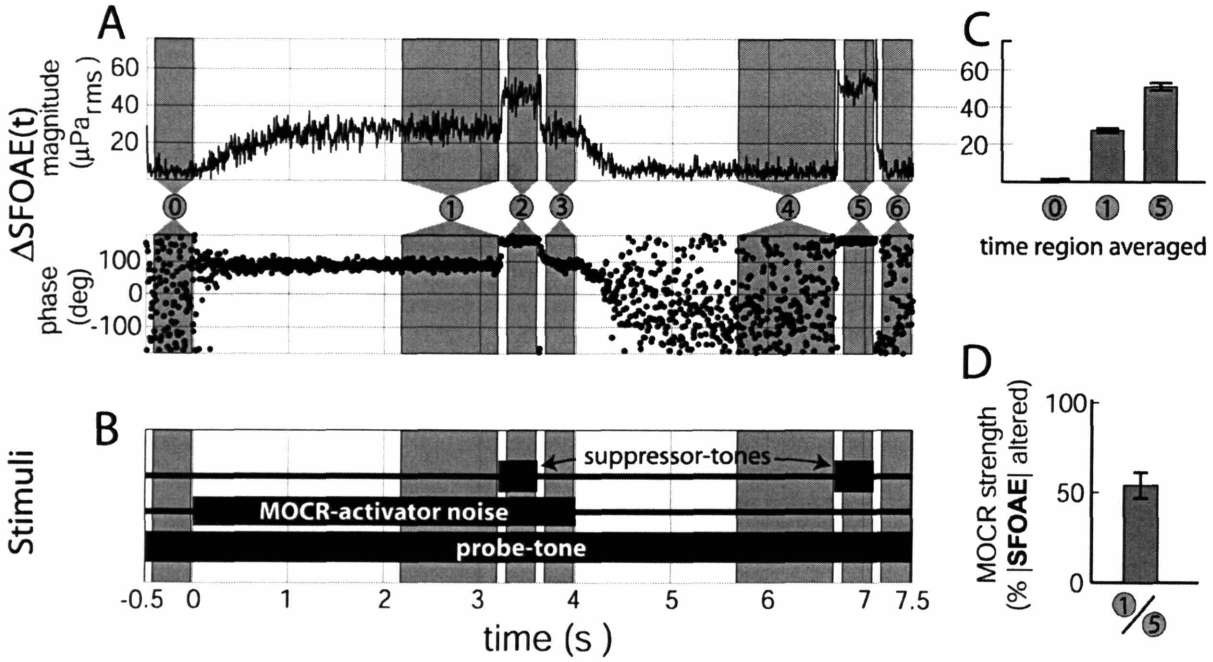

Figure 32. Stimuli (Panel B), response (Panel A), and analysis (Panels C and D) from a single measurement (vector average of all trials) used to quantify MOCR strength . Panel B displays the timing of stimuli used for all measurements (horizontal black bars). The probe-tone was a continuous, bilateral, 40 dB SPL, tone between 0.90 - 1.1 kHz. The MOCR-activator was a contralateral, 60 dB SPL, wideband (100 Hz - 10 kHz), 4 s, noise burst (0 ms < t < 4000 ms). Suppressor-tones (3200 ms < t < 3600 ms and 6700 ms < t < 7100 ms) were identical ipsilateral 60 dB SPL tone bursts lasting 400 ms placed 110 Hz below the probe-tone frequency. MOCR-activators and tone-suppressor had a 5 ms raised cosine rise/fall times and were alternated in polarity on successive buffers to cancel acoustic contributions. Panel A shows the change in ear-canal sound pressure at the probe tone frequency (1000 Hz in this case) over time, ΔSFOAE(t), during the 8 s repetition period. ΔSFOAE(t) responses were vector time-averaged across the following numbered regions to assess: 0. Noise floor, 1. MOCR response A, 2. combined two-tone suppression and MOCR response, 3. MOCR response B (control), 4. Noise floor B (control), 5. two-tone suppression (for SFOAE estimate), 6. Noise floor C (control). Panel C is a bar plot of the vector time-averages from this measurement for the noise floor (region 0), MOCR effect (region 1), and two-tone suppression effect (region 5). Error bars represent 95% confidence intervals about the means. The bar representing the noise floor is the mean noise + its 95% confidence (2 SDs) rather than the mean alone because the level was used to determine significant signal to noise separation. Panel D shows the normalized MOCR strength calculated from the measurement as the ratio of the MOCR effect to the two-tone suppression effect, error bar = 1 SE. Subject F150R.

D. Analysis

The magnitude and phase of the ear canal sound pressure at the probe frequency was extracted by first averaging an even number of burst responses (8-284 depending on subject response) and then heterodyning the averaged waveform (Kim, Dorn et al. 2001; Guinan, Backus et al. 2003). The change in the ear canal sound pressure over time due to the change in the SFOAE, **ΔSFOAE**(t), was calculated by vector subtraction of the pre-elicitor baseline average (-420 ms < t < 20 ms) from each time point. Vector time-averages of **ΔSFOAE**(t) were made for 7 time windows to quantify: (1) the MOCR raw effect

(shaded region #1 in Figure 32), (2) the SFOAE amplitude (from the two-tone suppression effect, shaded region #5 or #2 in Figure 32), (3) the noise floor, and (4) various measurement controls (shaded regions #0, #3, #4 and #6 in Figure 32). Values reported for MOCR raw effects, SFOAE estimates, or noise floor estimates are the magnitudes of the respective vector time-averages[49] described above, e.g. MOCR raw effects were quantified as

$$MOCR\ effect = \left| \frac{\sum_{t=2680ms}^{3680ms} \Delta\mathbf{SFOAE}(t)}{number\ of\ time\ samples} \right| \quad (1)$$

In order to estimate standard errors (SEs), a bootstrap technique was used[50]. For the bootstrap, the 'N' vectors averaged while computing an SFOAE estimate, noise floor estimate, or MOCR effect (e.g. Eq. 1), were pooled. Statistically similar data sets were then generated by taking N samples at random with replacement from the pool. 1000 such sets were generated. These sets were used to compute 1000 new estimates (of an SFOAE estimate, noise floor estimate, or MOCR effect) and their standard deviation was used as the estimate of the SE.

E. Normalization for MOCR strength

Since SFOAEs are measured in the presence of the probe-tone frequency, it is not possible to measure the native SFOAE alone. This is an issue because (a) SFOAE amplitudes vary across ears and frequencies and (b) weak SFOAEs produce small MOCR raw effects, but small MOCR raw effects do not necessarily indicate weak MOCRs (Figure 33). Consequently, when measured via SFOAEs, MOCR measures require normalization to compare across subjects.

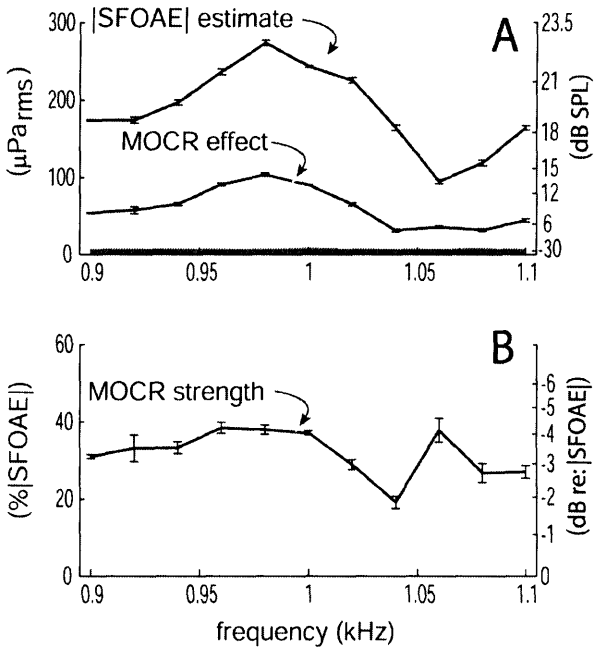

Figure 33. Estimated amplitudes of SFOAEs across frequencies from subject F156R compared to the effect of activating the contralateral MOCR (Panel A) show that these measures co-vary suggesting a normalization method for MOCR strength measures. Panel B shows the result of normalization (MOCR raw effect / |SFOAE| estimate). SFOAE amplitudes were estimated via two-tone suppression (see text). Probe-tones were continuous bilateral 40 dB SPL tones. Suppressor-tones were 400 ms (5 ms rise fall), 60 dB SPL tones placed 110 Hz below the probe-tone frequency. Contralateral MOCR activators were 2.5 s, 60 dB SPL wideband noise bursts. Error bars are +/- 1 SE.

Normalization is based upon the concept that measured MOCR raw effects, measured as **ΔSFOAE**(t) during MOCR activation, are a product of MOCR strength and SFOAE amplitude[51] i.e.

$$|\mathbf{SFOAE}| \times \text{MOCR strength} = |\Delta\mathbf{SFOAE}| \quad (2)$$

Normalization necessitated estimating native SFOAE amplitudes. We used two-tone suppression techniques (Shera and Guinan 1999) to suppress SFOAEs (e.g. region 5,Figure 32)[52]. Ideally if the

[49] Averaging within time windows took place after all trials constituting a measurement were averaged.

[50] The SE of the magnitude of a 'mean vector' depends upon its constituent magnitudes and phases and cannot be calculated in the same way as the SE of the mean of real-valued numbers. The bootstrap estimate of SE had the advantage that it required no assumptions about the underlying magnitude and phase distributions and how they were coupled.

[51] This concept is tacitly used by those who report MOCR strength as a dB change in other emission types (TEOAES or DPOAEs) where the native emission is measured directly.

[52] The combined MOCR/two-tone-suppression effects (region 2, Figure 1) were generally statistically indistinguishable from the two-tone suppression effect alone (region 5, Figure 1) at our stimulus levels; however,

SFOAE is completely suppressed, its amplitude equals the change in ear-canal sound pressure due to the suppressor-tone (e.g. average from window 5 in Figure 32). After normalization, the amount of MOCR inhibition[53] (of a given SFOAE) is expressed in %|SFOAE|.

III. RESULTS

The results are presented in 2 forms. First raw, un-normalized results (i.e. MOCR *raw effects*) are presented to demonstrate the ability to measure MOCR raw effects using this technique (Results A, B). Second, normalized results (i.e. MOCR *normalized effects*) are presented to investigate the variation of the MOCR strength within and across subjects (Results C, D, E). We make a distinction between measured MOCR *raw effects* and computed MOCR *normalized effects*.

The term 'MOCR *strength*' (first mentioned in Methods E.) is re-introduced later in the manuscript. It is reserved for discussing a property of the MOCR, and is not discussed until other factors that effect the measurements have been accounted for.

A. MOCR effects could be measured in 25/25 subjects

We were able to measure statistically significant (P = 0.05) MOCR raw effects for all ears, although not all frequencies in all ears produced significant raw effects. Figure 34 shows MOCR raw effects relative to the noise floor from all 25 subjects[54]. Each subject was measured at two frequencies, 1 kHz (Figure 34, Panel B) and a frequency that produced a comparatively large SFOAE within 10% of 1 kHz (except subject M166* who was measured at 1 kHz in the left and right ears) (Figure 34, Panel A). Ear F152L measured with a 1 kHz probe-tone and ear F149R measured with a 940 Hz probe-tone did not generate significant effects (Figure 34, far right). These subjects had very weak SFOAEs between 900 and 1100 Hz but both were ultimately measurable, at 900 Hz and 1 kHz respectively. The weakest responder, F149R, required 284 trials or 38 minutes of averaging time to demonstrate a significant (P=0.05) effect.

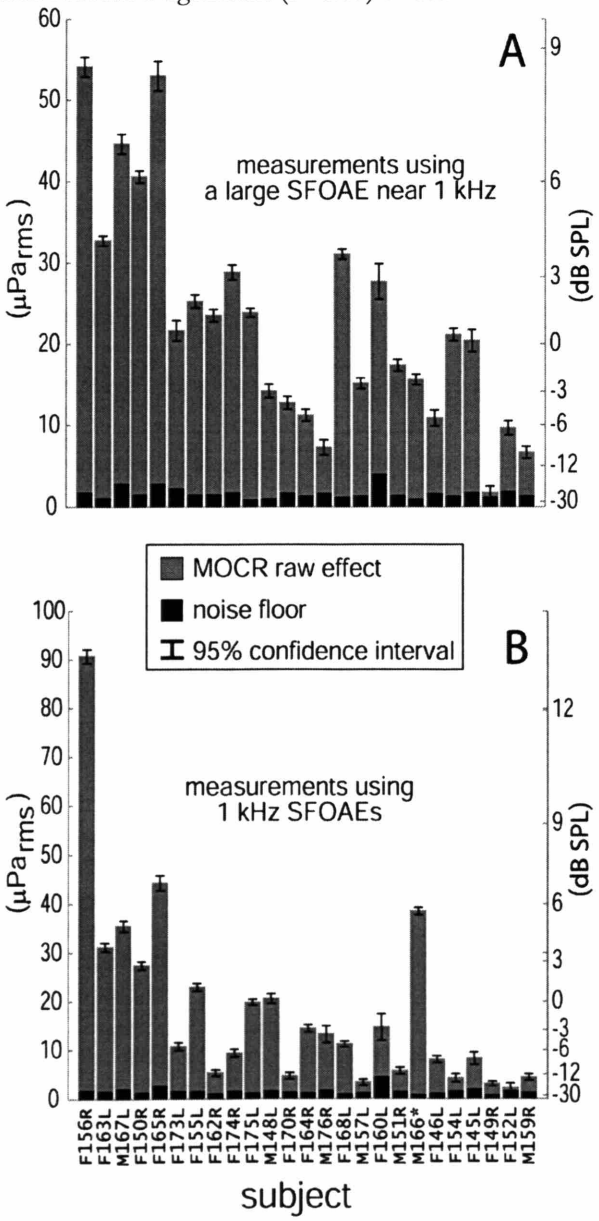

Figure 34. Plots of the magnitudes of MOCR raw effects on SFOAEs (grey bars) relative to measurement noise (black bars) from two SFOAEs measured in each of 25 subjects. Although not all ears could be measured at all frequencies, all ears registered statistically significant (P = 0.05) MOCR raw effects on at least one SFOAE near 1 kHz. Panel A are measurements of MOCR raw effects made using a large SFOAE (estimated from two-tone suppression) between 900 - 1100 Hz for each subject (excluding 1 kHz). Panel B shows MOCR raw effects measured in the same subjects using 1 kHz SFOAEs. F or M prefix indicates male or female, L or R suffix indicates left or right ear;

F168L's combined effect was significantly larger then her two-tone-suppression effect alone. For estimates of the native SFOAE we used the larger value from the 2 regions because our goal was to estimate the total |SFOAE|.

[53]Studies involving TEOAEs and DPOAEs show that emission amplitude is generally reduced, consistent with the observation that MOC activation reduces BM motion in response to sound.

[54] The subjects are arranged from left to right in decreasing order of total native |SFOAE| combined between the two SFOAEs measured (|SFOAEs| are not shown).

subject M166* was measured at 1 kHz in both the left (top) and right (bottom) ears.

B. Activating the MOCR generally changed native SFOAE amplitudes by 30%

Activating the MOCR with 60 dB SPL wideband noise generally resulted in a ~30% change in SFOAEs (Figure 35). However, MOCR effects on SFOAEs were scattered, displaying significant variation about a generally linear relationship[55]. Measurement noise was too small to account for these variations; they could be due to (1) inter-subject variation in MOCR strength or (2) other forms of variability including frequency-dependent variation and time-dependent variation.

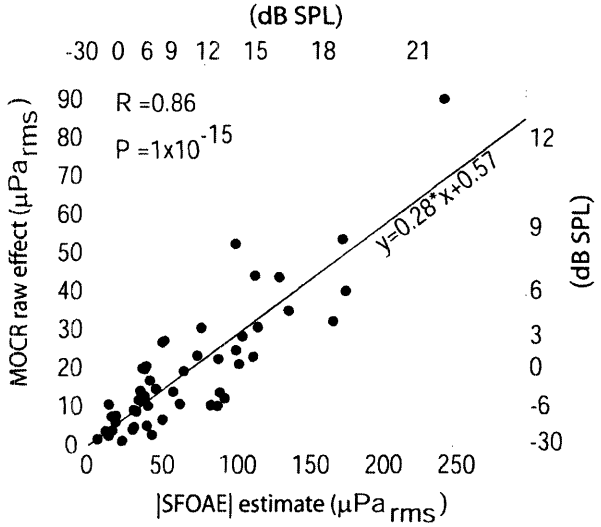

Figure 35. Plot of SFOAE amplitudes vs. MOCR raw effects on those SFOAEs shows that most SFOAEs are changed by ~30% during contralateral MOCR activation with 60 dB SPL wideband noise. All error bars are smaller than, and obscured by, the points used to represent the data, indicating that the departures of the points from the linear relationship are not due to measurement noise. Correlation (R = 0.86) was highly significant (P = 1e-15). Line represents a linear regression fit to the data (slope = 0.28 +/- 0.02, intercept = 0.57 +/- 2.05).

C. Measuring the MOCR strength in individuals

Hereafter, the results are reported as MOCR *normalized effects* (see Methods E). By normalizing MOCR effects on SFOAEs by their respective SFOAE amplitudes, a measure of MOCR normalized effects—expressed in terms of the percent of the SFOAE amplitude altered by MOCR activation—was made.

When we set out to quantify the distribution of MOCR *strengths* across normal-hearers, we presumed that MOCR *normalized effects* at one frequency would be similar to those normalized effects computed for nearby frequencies. Thus, we presumed that computing an MOCR normalized effect from measurements made at a single SFOAE frequency would be sufficient to quantify MOCR *strength*. Based on this assumption, we did not gather high-resolution data at many SFOAE frequencies, but chose to focus on just 2 frequencies near 1 kHz for each subject.

1. Single-frequency MOCR normalized effects at nearby frequencies showed little or no correlation

Two measures of MOCR normalized effects were computed for each subject from 2 high-resolution (8-284 averages) measurements using two different SFOAEs in each subject: (1) the 1 kHz SFOAE, and (2) a large SFOAE within 10% of 1 kHz (Figure 36). The two MOCR normalized effects were statistically uncorrelated (R=0.24, P = 0.27) which was surprising considering our initial assumption that MOCR strength would not depend strongly upon frequency. The source of the observed variation between the two measures was probably *not* due to subject arousal or other time-dependent factors because trials constituting the two measures were presented interleaved in time to remove time-dependent variations (8 – 284 trials were averaged depending on SNR and subject availability).

[55] Attempts to fit the data with power functions did not reveal an exponent significantly different from 1.

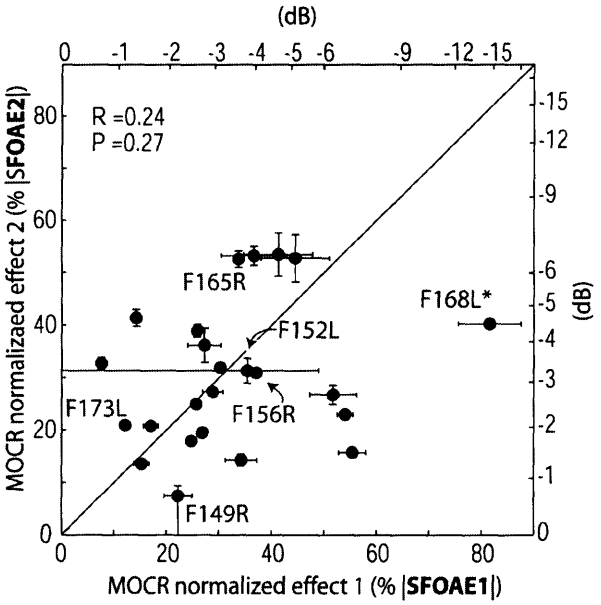

Figure 36. Two SFOAE-based measures of MOCR normalized effects (using 2 different SFOAE frequencies) for each of 24 subjects plotted against each other. The two measures were not significantly correlated (R = 0.24, P = 0.27) even though they were made over the same time, in the same ear, and at nearby SFOAE frequencies. 'SFOAE1' used the 1 kHz SFOAE, and 'SFOAE2' used a large SFOAE within 10% of 1 kHz. Error bars are +/- 1 SE; but most error bars are obscured by the data points. Subjects that are referred to in the text are labeled here and in subsequent graphs. Subject F152L and F149R have asymmetric error bars that reach to zero because a statistically significant MOCR raw effect was not measured at 1 SFOAE frequency for these subjects (see Figure 34). Subject M166* from Figure 34 is not included in this plot because the 2 measurements made with this subject were not in the same ear. When subject F168L* is excluded from R and P value calculations (because these calculations are sensitive to outliers) R = 0.18, P = 0.41.

Figure 36 shows no evidence that systematic bias was introduced by electing to measure at large SFOAEs near 1 kHz as opposed always to selecting 1 kHz always. Data from the two measures were statistically indistinguishable, i.e. data were scattered equally above and below the line y=x with measure 1: mean = 32%, SD = 17%, SE = 3.4%; measure 2: mean = 31%, SD = 13%, SE = 2.6%. The standard deviation of the MOCR normalized effects measured using the largest SFOAE near 1 kHz (measure 2) was 4% less than measure 1's, hinting that larger SFOAEs may provide more consistent measures.

2. *MOCR strength measures varied significantly with SFOAE frequency*

Since we found little or no correlation between nearby single-frequency MOCR normalized effects, it behooved us to look across multiple frequencies.

Although we only took high-resolution measurements (8 - 284 averages w/interleaved trials) at two frequencies per subject, we did take low-resolution measurements (4 averages w/non-interleaved trials) at 11 SFOAE frequencies near 1 kHz (900 - 1100 Hz, 20 Hz steps, measured in randomized order) for each subject. The following results are taken from this low-resolution dataset.

Figure 37 shows how MOCR normalized effect varied across frequency and time in 2 ears—trials forming these measurements were not interleaved and the curves contain undiminished time-dependent variations as well as frequency-dependent ones (see Appendix A). Similar variations were found in all subjects (avg. SD across frequency = 15%, min SD = 3.3%, max SD = 36%). Variations were evident in both high and low SNR measurements; however, subjects with consistently large SFOAEs (and therefore high SNRs) tended to produced more consistent measurements across frequency and time.

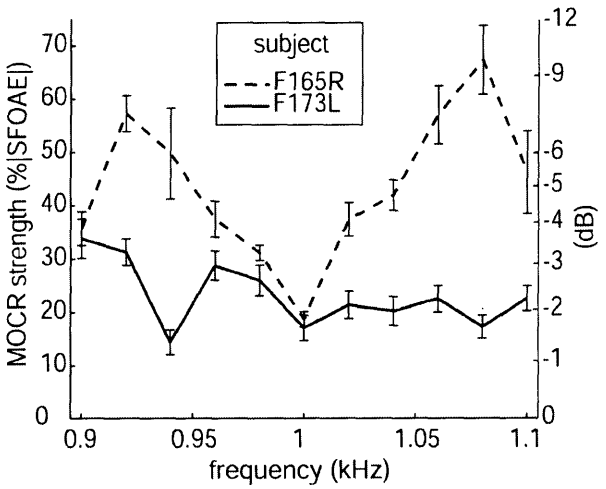

Figure 37. MOCR strength measures at various frequencies (measured using different SFOAEs) for 2 subjects show subject-specific frequency-dependent variation. Variations like these were typical of all subjects. Error bars indicate +/- 1 SE.

In order to reduce frequency-dependent and time-dependent variation and establish measure of a subject's regional (near 1 kHz) MOCR *strength*, the low-resolution measurements in each subject, made at different SFOAE frequencies (11 frequencies between 900 – 1100 Hz with 20 Hz spacing) were averaged. MOCR raw effects were normalized to produce *normalized effects* for each frequency at which both the

mean MOCR raw effect and the mean |SFOAE| estimate were 2 SDs larger than the mean measurement noise. From these ~11 single-frequency MOCR normalized effects, two groups were formed: (1) the ~6 measures <= 1 kHz and (2) the ~5 measures > 1 kHz[56]. The measures were averaged within their group resulting in 2 frequency-averaged regional MOCR *strength* measures for each subject—one centered ~50 Hz below 1 kHz and one centered ~50 Hz above 1 kHz, both spanning ~100 Hz.

Figure 38 shows that the frequency-averaged MOCR strength measures were correlated (R = 0.47, P = 0.022). The two measures were also statistically indistinguishable (measure 1: mean = 29%, SD = 13%; measure 2: mean = 31%, SD = 15%). The measures spanned 5% to 64%, and tended to move together suggesting that a portion of the spread was due to inter-subject variation. In conclusion, when several single-frequency MOCR normalized effects were averaged, frequency and time-dependent variations were reduced enough to produce correlated *regional* (around 1 kHz) MOCR *strength* measures in a given subject.

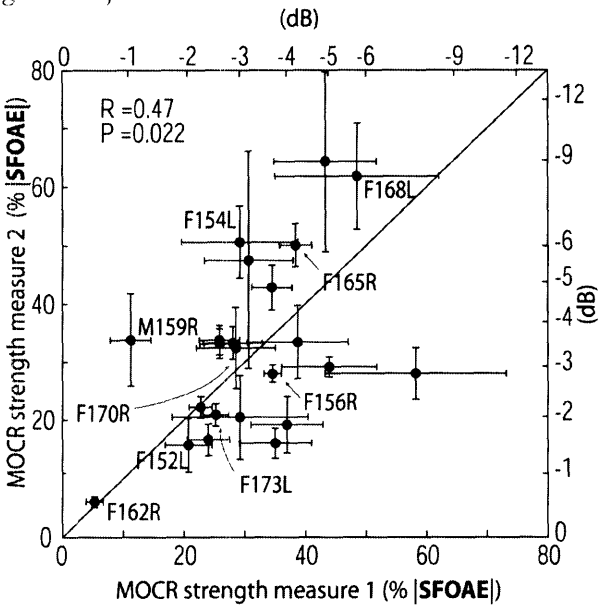

Figure 38. Two frequency-averaged SFOAE-based measures of MOCR strength from each of 23 subjects plotted against each other. The two measures of MOCR strength are correlated (R=0.47, P = 0.022) and spanned a range from 5 - 64%, indicating there are statistically significant inter-subject variations in MOCR strength. Measure 1 was an average of 2-6 (depending on measurement noise) SFOAEs between 900-1000 Hz inclusive; measure 2 was an average of 2-5 SFOAEs between 1020-1100 Hz inclusive (20 Hz steps). Error bars are +/- 1 SE. Two subjects: M166* from Figure 34, and F149R who did not yield an MOCR measure 2 above the noise floor, are not included.

D. Comparison of subjects' regional MOCR strengths measured by (1) combining low resolution data from ~11 SFOAEs vs. (2) combining high resolution data from 2 SFOAEs

The high-resolution dataset (reported in Results C) and low-resolution dataset (reported in Results D) both contained information about a subject's regional MOCR strength. Although the two sets had measurements from SFOAEs at some of the same frequencies, they were independent in the sense that they did not share any trial presentations. In order to provide the 'best estimate' of the regional MOCR strength (near 1 kHz) for each subject the datasets were compared and ultimately combined.

Each dataset was used to produce one estimate of a given subject's regional MOCR strength. For the low resolution data, all single-frequency MOCR normalized effects that were 2 SD above the noise floor (for a given subject) were averaged. For the high resolution data, the two single-frequency MOCR normalized effects (plotted in Figure 38) were averaged.

Figure 39 shows that the two estimates described above are correlated (R = 0.72, P = 0.0001) indicating that they share information about a subject's regional MOCR reflex strength. Some correlation was expected because the high-resolution dataset contained measurements at SFOAE frequencies that were a subset of those measured in the low-resolution dataset. A least squares linear regression fit through the data points in Figure 39 confirms that the relationship is essentially 1:1 ($y = 0.83\pm0.06x + 6.4\pm1.4$). The R^2 value, commonly used to account for variance, suggests that a majority of the variance ~52% could reasonably be ascribed to inter-subject variation.

[56] Some low SNR subjects did not generate all 11 measures. The following 6 subjects had less than 3 measures to average for at least 1 group: F149R, F152L, F154L, M159R, M166, F162R.

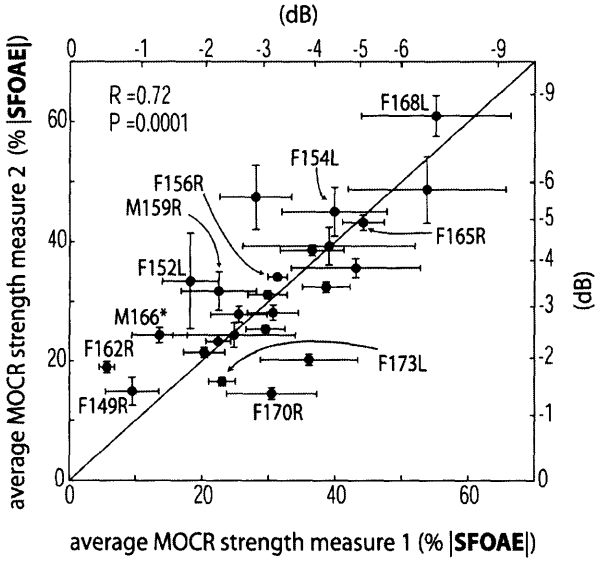

Figure 39. Two estimates of regional MOCR strength near 1 kHz for each of 24 subjects plotted against each other. The two estimates are significantly correlated (R=0.72, P = 0.0001) and spanned a range from 5 - 61%, indicating there is statistically significant inter-subject variation in regional MOCR strength near 1 kHz. Measure 1 was an average involving 3-11 (depending on measurement noise) SFOAEs between 900-1100 Hz inclusive (20 Hz steps); measure 2 was an average involving 2 SFOAEs between 900-1100 Hz inclusive. Error bars are +/- 1 SE. Subject M166* from Figure 34 was not included because his measurements were not all in the same ear.

Although Figure 36 shows that a subject's regional MOCR strength cannot be reliably measured via a single-frequency MOCR normalized effect, it appears that averaging across as few as two single-frequency measures can begin to show a subject's regional MOCR strength, particularly for subjects with large SFOAEs, i.e. those with small error bars in Figure 36.

E. The distribution of MOCR strengths across subjects

In order to generate a single best estimate of MOCR strength for each subject, the average of the 2 estimates for each subject from Figure 39 was computed. Figure 40 shows our best estimate of MOCR strength for 24 normal-hearing subjects (Panel A) and a histogram of the distribution of MOCR strengths across those subjects (Panel B). High SNR subjects produced MOCR strengths slightly lower than low SNR subjects (12 high SNR subjects: mean = 29.5%, SE = 2.6%; 12 low SNR subjects: mean = 32.8%, SE = 3.8%) but the difference was not significant indicating that there is no significant SNR-related bias. The distribution was relatively symmetrical, but subject F168L had a strong effect on the symmetry as calculated by skewness. Skewness with and without subject F168L was 0.47 and 0.13 respectively.

In general, MOCR activation with a 60 dB SPL contralateral wideband noise[57] altered a subject's SFOAEs by 30% (mean = 30.6%, SD = 11.2%); regional MOCR strengths spanned a range from 12% to 58%.

[57]The sound level and bandwidth of the noise used to activate the MOCR has a direct impact on MOCR strength measured this way

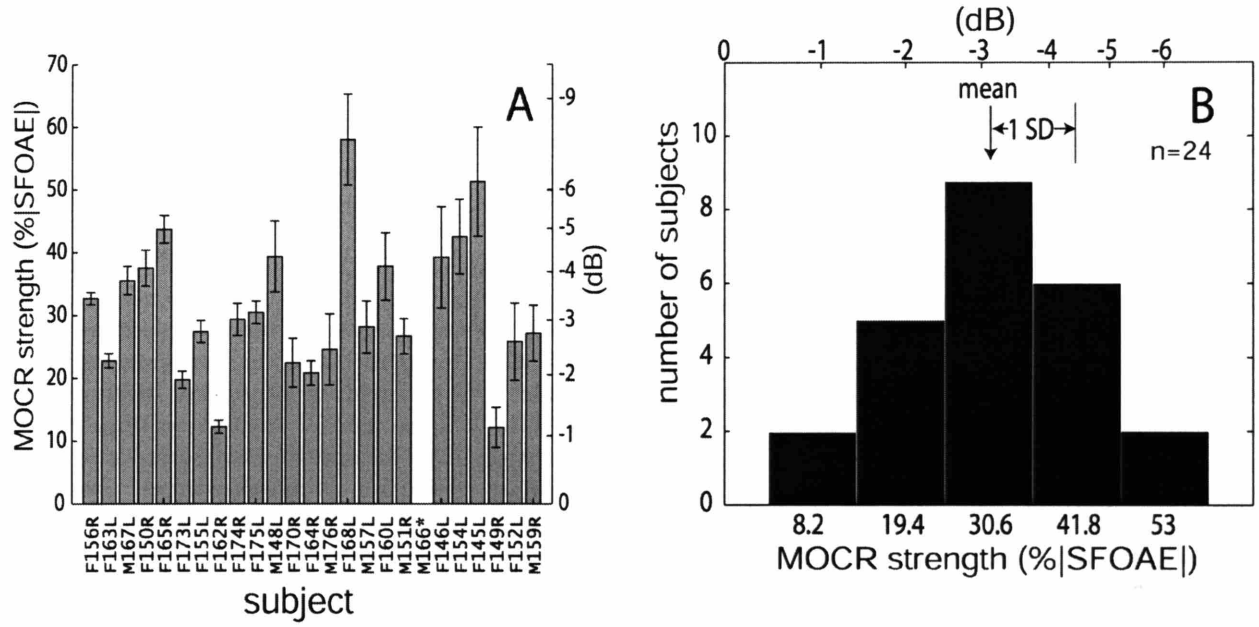

Figure 40. Panel A: best estimates of regional MOCR strength near 1 kHz for 24 normal-hearing subjects tested; Panel B: distribution of regional MOCR strengths across subjects (mean = 30.6%, SD = 11.2%). MOCR activation with contralateral 60 dB SPL wideband noise generally suppressed SFOAEs near 1 kHz in a given subject by 30% (range = 12 - 58%). Error bars are +/- 1 SE, and reflect the uncertainties in the measurement. Subject M166* was omitted because not all his measurements were made in the same ear.

IV. DISCUSSION

A. Frequency-dependent variations: implications for understanding how the MOCR changes SFOAEs

Single-frequency MOCR normalized effects were found to have a subject-specific, frequency-dependent variation as well as a time-dependent variation (see Appendix A). Two single-frequency MOCR normalized effects measured in the same ear at nearby frequencies—using SFOAEs near 1 kHz that differed by as little as 40 Hz—were found to be statistically different.

These fine-scale frequency-dependent variations were surprising because initially we believed that:

"MOCR activation causes a 'constant fraction' reduction in cochlear amplifier gain and this reduction is solely responsible for changing SFOAEs."

We assumed 'constant fraction reduction' because the cochlear gain region for a 1 kHz tonal input is limited, a common estimate is about 1/3 octave, and single MOCR fibers have been shown to span 10ths of an octave to a full octave (Liberman and Brown 1986; Brown 1989). We reasoned that activating many fibers with a wideband elicitor would 'blanket' the gain region resulting in a constant fraction reduction of gain across the gain region. In addition, the SFOAE reflection mechanism (Zweig and Shera 1995) was assumed to be unaffected by MOCR activation (i.e. the factors involved in determining reflections were assumed unchanged). Consequently, we presumed that changes in SFOAEs were a direct result of uniform gain reduction, and would therefore not vary with frequency (or more realistically only vary slowly with frequency). In simplified conceptual mathematical terms we believed:

$$\Delta\mathbf{SFOAE}(f) = MOCR\ strength \cdot |\mathbf{SFOAE}(f)| \quad (3)$$

$$|\mathbf{SFOAE}(f)| = gain(\frac{f}{CF}) \cdot reflection\ factors(CF) \quad (4)$$

$$\Delta\mathbf{SFOAE}(f) = MOCR\ strength \cdot gain(\frac{f}{CF}) \cdot refl.\ factors(CF) \quad (5)$$

Our finding that single-frequency MOCR normalized effects vary abruptly with frequency invalidated the concept in (1), and challenged the individual assumptions that created it. In response, we hypothesized new mechanisms to account for the finding.

(1) 'Constant fraction' gain reduction may not hold. If MOCR activation changes the gain function, g(f/CF), in a frequency or characteristic frequency (CF) specific way, the shape of the BM traveling wave (i.e. the magnitude envelope and/or phase profile across f/CF) would be altered. Gain reduction would still make less energy available for reflection as mentioned in (1), but in addition, since SFOAEs are thought to be sensitive to the magnitude and especially phase (via requiring coherent reflections) these magnitude and phase changes would produce a separate change in the SFOAE—one that varies with frequency.

(2) SFOAE reflection factors may be affected. SFOAEs are thought to be a result of tiny reflections from micro-scale impedance discontinuities (Zweig and Shera 1995). If MOCR activation changes the properties of OHCs (such as their gains) in a way that alters those discontinuities, SFOAEs would theoretically be affected in a frequency-dependent way.

Averaging across frequency reduced both the frequency and time-dependent variations and left a robust MOCR effect. Whatever the mechanisms that produce the fine-scale frequency changes are, the remaining normalized effect after they are removed is presumed to be due to MOCR-induced changes in the cochlear amplifier gain. If this is true, it is appropriate to call the remaining effects MOCR *strength* as we have done here.

B. Regional MOCR strength

Averaging across several single-frequency MOCR reflex measures (spanning ~100 Hz, near 1 kHz) reduced the fine-scale frequency-dependent variations enough to reveal that there are subject-specific *regional* MOCR strengths that vary slowly enough with frequency to make adjacent 100 Hz frequency-averaged measures of regional MOCR strength correlated. The extent to which these regional MOCR strengths are representative of a subject's 'overall' MOCR strength, where 'overall' strength means the strength averaged across all frequencies in the hearing range, is not known.

Our best estimate of each subject's regional MOCR strength near 1 kHz shows that a range (12% - 58%) of regional strengths exists in the normal-hearing population. Furthermore, the shape of the histogram in Figure 40 suggests that the data could easily come from an underlying normal distribution. A Shapiro-Wilk W test for normality reinforces this idea: $W = 0.97$, $P = 0.68$; by contrast a $P < 0.05$ would indicate the sample distribution is likely from a non-normal underlying distribution. In short, the underlying population distribution could easily be normal with a mean near 30% and an SD ~10% (for 60 dB SPL contralateral wideband noise MOCR activators.

We acknowledge that our measure of MOCR strength is not ideal, and not all of the variability in Figure 40 is necessarily due to inter-subject variation of MOCR strengths but it is the best measure available. Our comparison of several measures of regional MOCR strength for each subject (Figures 38, 39) indicates that a majority of the observed variability in our final distribution is from inter-subject variation, not measurement noise, frequency variation or time variation.

C. Comparison with prior work

Although previous data containing OAE-based measures of MOCR strengths across adult populations exist (Micheyl, Morlet et al. 1995; Maison, Micheyl et al. 2000; De Ceulaer, Yperman et al. 2001), it is difficult to compare these prior results with our results because different methods and OAE types were used. Before comparing the data, the methodological differences between these 4 studies (and how the histograms were generated) are outlined below.

1. TEOAE MOCR strength measures from De Cuelaer et al. (2004) and Micheyl et al. (1995)

The main differences between the TEOAE-based measures of De Cuelaer (2001) and Micheyl (1995) and ours are (1) the use of TEOAEs (2) no FFT used during analysis. At first, this method appears comparable to ours in that (1) humans were measured, and (2) TEOAE time responses appear to be simply the inverse FFT of component SFOAEs (Kalluri and Shera 2004). However, by analyzing and reporting dB suppression of TEOAEs purely in the time domain, these measures are affected by changes in the relative phases of SFOAE components caused by MOCR activation. The effect of MOCR activation on SFOAE phase is complex and not well understood. In addition, the TEOAE-evoking stimulus is likely to have activated the ipsilateral MOCR and how that interacts with the contralateral MOCR is unknown. Also the click levels used in the De Cuelaer et al. study (2001) may have been high enough to produce middle

ear muscle reflex (MEMR) effects that went unseen using a clinical MEMR test. Nevertheless, the dB suppression reported by these investigations are converted to % suppression and presented in Figure 41, Panels B and C.

2. DPOAE MOCR strength measure from Maison et al. (2000)

The main differences between the Maison et al. (2000) measure and ours are (1) the use of guinea pigs, (2) the use of distortion products, and (3) the use of the adaptation method[58]. The use of DPOAEs complicates the interpretation of MOCR strength measures because DPOAEs are known to be composed of 2 emissions components (Shera and Guinan 1999), but just how activating the MOCR interacts with those components is not well understood[59]. The use of the adaptation method also complicates the interpretation of MOCR strength because the loud primary tones used to generate DPOAEs may activate local intrinsic cochlear effects in addition to MOCR mediated ones (Guinan, Backus et al. 2003).

In order to translate the MOCR strength reported by Maison et al. (2000) as 'dB strength' into a histogram on a scale that would be comparable to our %|SFOAE| scale, we ignored the fact that their dB measure came from a very different method. Their method selected for maximum effects (suppression + enhancement) for each animal from a matrix of measurements made with different stimulus parameters thereby inflating the values. For comparison purposes we ignored the fact that reported dB values contained both observed suppression (reduced DPAOE during adaptation) plus enhancement (increased DPOAE during adaptation) and treated all the reported MOCR strengths as if they were dB of suppression (Figure 41, Panel D, top axis).

3. Comparisons of data from the 4 studies.

Since MOCR strength measures grow as an approximately linear function of elicitor level (see Chapter 3, Results B2), comparing across studies that use different MOCR activator levels, requires scaling. The data from De Cuelaer et al. (2004) and Micheyl et al. (1995) used the same TEOAE-based method, but different MOCR activator levels (40 dB SL CAS broadband noise, and 50 dB SPL CAS broadband noise respectively), and when scaled, it is highly likely that the distributions (Figure 41, Panels B, C) came from the same underlying distribution (A two-sided Kolgormorov-Smirnov test produces: D = 0.096, P = 0.99; by contrast a $P < 0.05$ indicates a significant chance the sample sets came from different underlying distributions). Furthermore the ratio of SD/mean for both datasets is 0.61. It is not surprising that these two distributions are similar given they measured both normal-hearing subjects in the same way.

There is an interesting difference between the TEOAE-based data discussed above and the SFOAE-based data presented here. A Shapiro-Wilk W test on De Cuelaer's data suggests that the TEOAE-based data could not easily come from an underlying normal distribution (W = 0.96, P = 0.06—a $P < 0.05$ indicates the sample distribution is very likely from a non-normal distribution[60]). However, the same test on our SFOAE-based data does not show evidence of non-normality (W = 0.97, P = 0.68), although more data could potentially show non-normality. Furthermore, the SD/mean for the SFOAE-based data was 0.36 vs. 0.61 for the TEOAE-based data, indicating that there was a different relationship between the mean and spread of the data in each case. The two measures of MOCR strength are not giving statistically compatible MOCR strength results.

The source of the discrepancy is probably methodological. One issue is that if only suppression is measured, a lower bound of 0% (or 0 dB) is enforced on all data. The fact that the TEOAE data falls near this lower bound may help explain the positive skew (Figure 41, Panel B's skewness = 0.68). Another explanation is that noise is introduced in the TEOAE-based method by MOCR-induced phase changes that have an effect on the measure as a result of the analysis being carried out in purely the time domain. Finally, our SFOAE-based measure only captures the regional MOCR-strength near 1 kHz. It is not clear how to compare regional MOCR strengths to TEOAE-based MOCR strength measures because the frequencies that are primarily responsible for determining the TEOAE-based results are not identified.

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[58] The adaptation method measures the ipsilateral, rather than the contralateral MOCR.

[59] The fact that DPOAEs arise from multiple components may help to explain why MOCR activation can enhance as well as suppress DPOAEs.

[60] De Cuelaer et al. (2004) reported $P<0.05$, the difference is that they used their data in dB and we are using the data transformed into % which reduces positive skew.

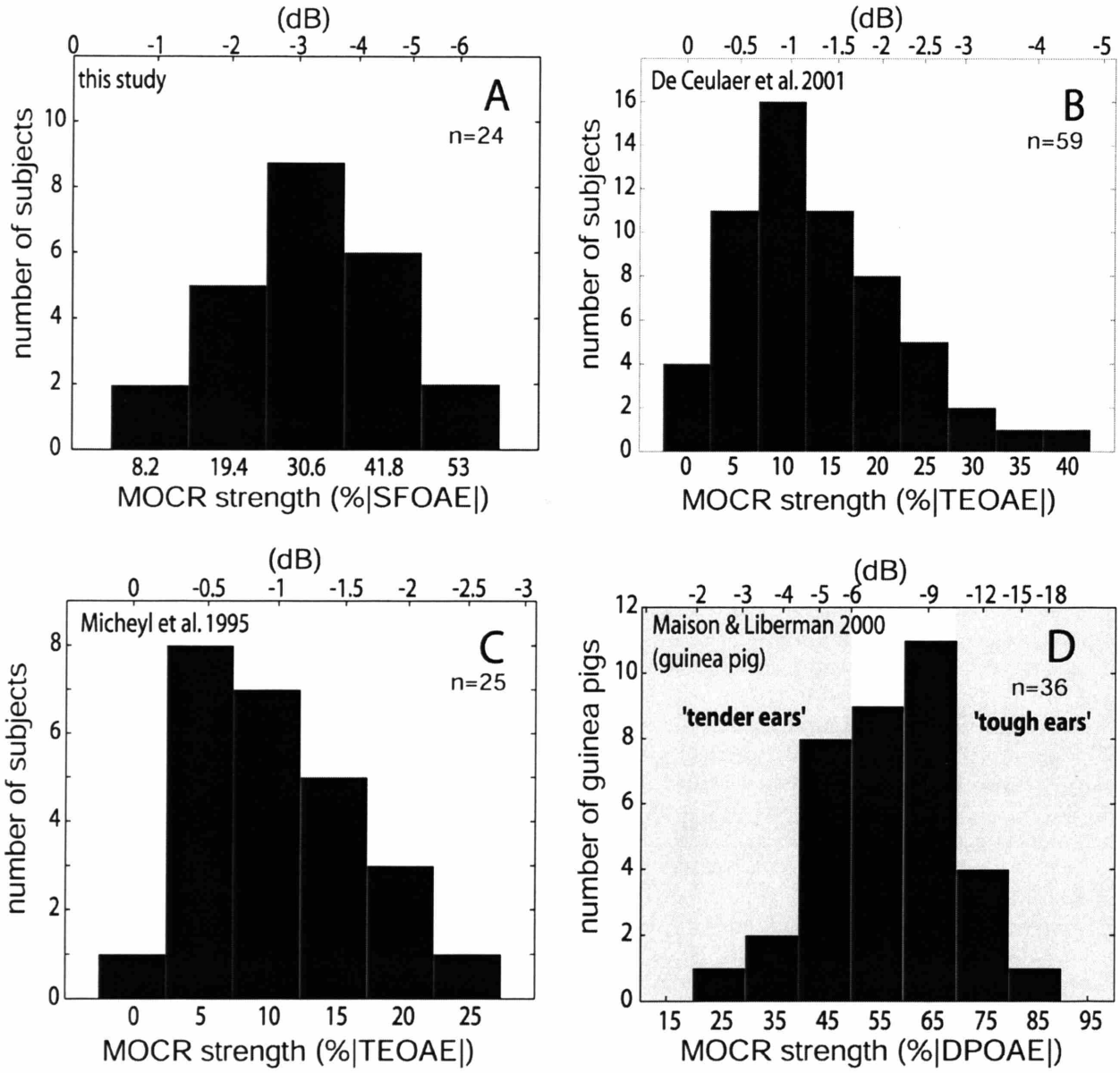

Figure 41. Histograms of MOCR strengths across adult populations adapted from the data in 4 studies using various OAE-based measures of MOCR strength. Panel A is data from this study. Panel B is adapted from De Ceulaer et al.'s (2001) TEOAE-based measures showing 59/60 normal-hearing humans (the 59 that showed TEAOE suppression to MOCR activation are plotted, 1 subject showed TEOAE enhancement and was omitted). Panel C is adapted from Micheyl et al.'s (1995) TEOAE-based measures in normal-hearing humans. Panel D is adapted from Maison et al.'s (2000) DPOAE-based measures in guinea pig. The grey bars indicate correlation of the measure with susceptibility to PTS. For details about how the histograms were generated from the raw data reported in the studies, see Discussion A.

DPOAE-based data from Maison et al. (2000) in guinea pig does *not* show evidence of non-normality (Shapiro-Wilk test: W = 0.976, P = 0.604), is not significantly skewed (skewness = -0.05), and has an SD/mean = 0.23. In these respects, the DPOAE-based measure in guinea pig is statistically more comparable with our SFOAE-based results than the TEOAE-based measures performed in humans.

C. Implications for susceptibility to acoustic trauma

There is evidence from cat and guinea pig that the MOCR affords protection from temporary threshold shifts (TTS) caused by to loud noise (Rajan and Johnstone 1983; Rajan and Johnstone 1988; Rajan 1995). The protective effect extends to permanent threshold shifts (PTS), and furthermore, it has been found in guinea pig that stronger MOCR reflexes afford greater protection against PTS (Maison and Liberman 2000). Figure 41, Panel D shows a histogram of MOCR strengths across 36 guinea pigs made from the data in Maison et al. (2000). Grey bands separate the measured ears into 3 categories: (1) ears that were most susceptible to acoustic trauma, 'tender' ears, (2) ears that were least susceptible 'tough ears' and, (3) an intermediate group.

If the human MOCR is similar, then comparing an individual's MOCR strength to a distribution of MOCR strengths taken from the normal-hearing population could reveal that individual's relative susceptibility to acoustic trauma, prior to any damage.

D. Using TEOAEs to measure MOCR strength, a suggested analysis method

Contralateral suppression of TEOAEs has been used to asses MOCR function throughout the literature. In scientific pursuits, the technique has been used when correlating MOCR function with psychoacoustic measures in an effort to determine what role in hearing the MOCR might play (Micheyl, Morlet et al. 1995). More recently these techniques have been applied to patient populations, for instance TEOAEs have been used to demonstrate that patients with CAPD (central auditory processing disorder)[61] have a reduced MOCR strength to go with enhanced native |TEOAE| levels relative to normal-hearers (Bar-Haim, Henkin et al. 2004). Normative data has been pursued (De Ceulaer, Yperman et al. 2001) (Figure 41, Panel B) in anticipation of the more widespread use of TEOAE-based assays of MOCR strength clinically, for evaluating tinnitus, susceptibility to acoustic trauma, and hyperacusis. But are these TEOAE-based measures that are being used the right ones?

It seems that TEOAE-based techniques are advantageous because they naturally contain multiple SFOAEs[62] and therefore frequency-dependencies (e.g. Figures 37, 42, 43) may be removed easily if the measurement is analyzed with this in mind.

The most common way to report MOCR strength via TEOAEs involves reporting the suppression of the time domain signal in dB. This time-domain signal, as mentioned above, is a complex of many frequencies adding with different phases and the consequence of activating the MOCR on the contributing phases is not well understood, so it is unclear what the reported amount of suppression in the time-domain means physically. A better way to analyze TEOAE data when assessing MOCR strength might be to take the FFT of the TEOAE before and during CAS and compute the average energy reduction across all frequency bins.

E. The gold-standard measurement of MOCR strength

Like other OAE-based methods, the SFOAE-based method presented here has limitations and complexities that prevent it from being an ideal measure of MOCR strength. The main difficulty is the strong frequency-dependent variations of the measure (Results B2), which may be due to how MOCR activation interacts with unique microstructure of a given cochlea—a problem shared among all OAE-based measures.

A better measure of a subject's MOCR strength would be a neural measure, e.g. measuring changes due to acoustic MOCR activation in compound action potentials (CAP) or wave 1 of the ABR response.

APPENDIX A: TIME AND FREQUENCY-DEPENDENT VARIATIONS CONTRIBUTE TO MEASUREMENT VARIABILITY

When measuring MOCR effects is important to appreciate the sources of variability in those measures. MOCR normalized effects have significant time and frequency-dependent variations (Figure 42) that have not been well appreciated.

[6] CAPD patients have particular difficulty hearing speech in noisy environments, may not have stapedial reflexes, and have learning disabilities.

[62] A TEOAE time response appears to be simply the inverse FFT of component SFOAEs for low sound levels (Kalluri and Shera 2004).

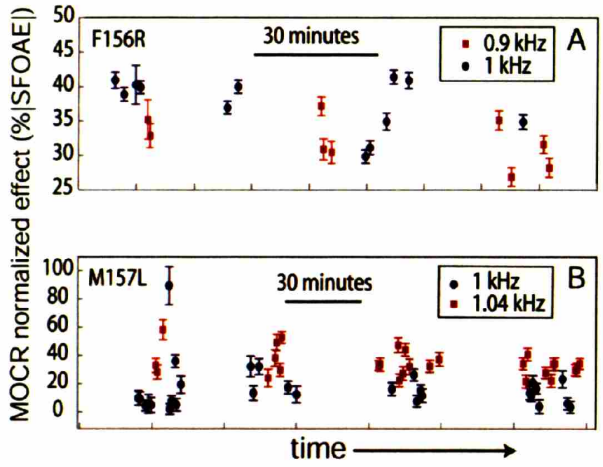

Figure 42. MOCR normalized effects on two nearby SFOAE frequencies (listed in kHz the legends) measured at different times for subjects F156R (Panel A) and M157L (Panel B). Panel A shows large time-dependent variation. Panel B shows a significant fine-scale (40 Hz) frequency-dependent difference. Error bars are 1 SE.

Figure 42, Panel A demonstrates the existence of a strong time-dependent variation that outstrips measurement error (error bars) for subject F156R. Subject F156R was the highest SNR subject, yet her normalized effect values, though measured at the same SFOAE frequency, changed over time, spanning a ~15% range. All subjects showed time variations. Time-dependent variations could be caused by slow MOCR actions with time constants of 10's of seconds that have been reported (Sridhar, Liberman et al. 1995) and are discussed in Chapter 3. The variations could also result from changing subject arousal or perhaps some time-varying change in SFOAEs from a non-MOCR mechanism. Whatever the cause, when measuring how MOCR activation affects SFOAEs, one must consider *time* a fundamental factor.

Figure 42 Panel B demonstrates the existence of fine-scale (in this case 40 Hz) frequency-dependent variations in MOCR responses for subject M157L. The ~18% difference between the means of the 1 kHz (blue) and 1.04 kHz (red) measures was statistically significant (1 kHz data: mean = 16.4%, SD = 16.8%[63]; 1.04 kHz data: mean = 34.3%, SD = 9.2%; Student's T-test: T = -4.9, P = 9e-6) and could not be explained by the time-dependent variation.

[63] When the 1 kHz outlier at ~90% was omitted from standard deviation calculations, SDs were quantitatively similar: 1 kHz data: SD = 9.26%; 1.04 kHz data: 9.22%, suggesting that the unknown process which produces the time-dependent variations might be the same at nearby frequencies.

Fifteen of 24 subjects demonstrated significant fine-scale (within 100 Hz) frequency-dependent variations by passing both a Student's T test (that determines whether there is a significant difference between means) and a Kolgormorov-Smirnov test (that determines whether datasets are from different underlying distributions[64]) with P values < 0.05. Larger differences between MOCR normalized effects were observed when the frequency separation between SFOAEs used in measuring them was larger (Figure 43).

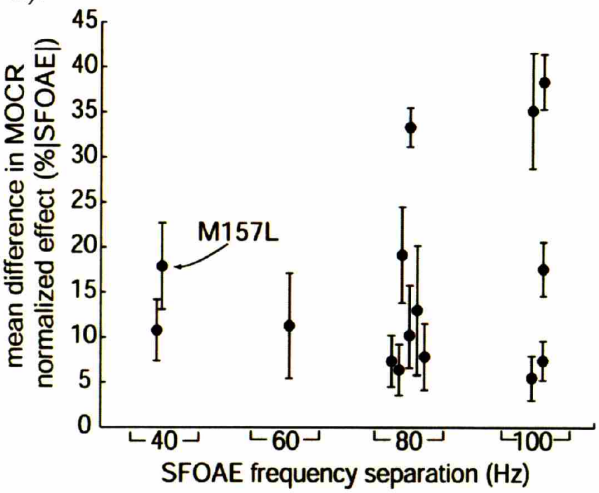

Figure 43. Differences in MOCR normalized effects (y-axis) due to measuring those effects with SFOAEs at different but nearby frequencies (with a frequency separation indicated by the x-axis) for 15 subjects. These 15 subjects are shown because each passed both a Student's T-test and a Kolgormorov-Smirnov test at the P = 0.05 level, indicating that the differences observed were significant ones, not due to time-dependent variation. Subject M157L is labeled to allow a comparison with the previous figure. Error bars are 1 SE of the computed difference.

The discovery of fine-scale frequency-dependent variation is new. Its source is unknown, but possible sources are discussed in Discussion A.

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[64] A Student's T-test assumes that the two distributions have equal variance. The KS test requires no such assumptions about the distributions.

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Chapter 6: Summary & Future Directions

ABBREVIATIONS

AC	alternating current
AM	amplitude modulation
DC	direct current
HF-AM	high frequency amplitude modulation (20 – 400 Hz)
IC	inferior colliculus
MOC	medial olivocochlear
MOCR	medial olivocochlear reflex
OAE	otoacoustic emission
SFOAE	stimulus frequency otoacoustic emission
TEOAE	transiently evoked otoacoustic emission
TTS	temporary threshold shift

I. THESIS REVIEW

Vertebrate animals send descending efferent input to their sensory organs that allows the adjustment of those biological sensors to changing environmental conditions. The medial olivocochlear reflex (MOCR) is one such auditory reflex (for a review see(Guinan 1996). when activated, the effect of the reflex is to reduce the gain of the ear by decreasing the mechanical response of the basilar membrane (BM) to sound (Murugasu and Russell 1996; Cooper and Guinan 2003). Currently, there is no consensus for the primary role of the MOCR in hearing.

The discovery of otoacoustic emissions (Kemp 1978) and the ensuing discovery that those emissions can be modified by activating the MOCR (Mountain 1980) gives us the tools needed to investigate basic properties of the MOCR non-invasively in normal-hearing humans.

The purpose of this thesis has been to quantify and discuss 4 basic properties of the MOCR using stimulus frequency otoacoustic emissions (SFOAEs): (1) the relative strengths of the ipsilaterally, contralaterally, and bilaterally activated reflex, (2) the time-course of the reflex (3) the efficacy of amplitude modulation (AM) for activating the reflex and (4) the distribution of reflex strengths within a normal-hearing population. Each property builds upon an existing literature and provides a point of discussion for the role the reflex may play in hearing.

II. SUMMARY OF FINDINGS AND FUTURE DIRECTIONS BY CHAPTER

A. Chapter 2: Relative strengths of the ipsilaterally, contralaterally, and bilaterally activated medial olivocochlear reflex

This chapter quantified and compared the relative strengths of activating the MOCR via its ipsilateral or contralateral pathways and demonstrated that the response magnitudes are, on average, equal near 1 kHz[65]. In addition, the sum of these two monaural responses, i.e. ipsilaterally and contralaterally-activated responses, was, on average, equal to the bilaterally-activated response at 1 kHz. Thus, no evidence of binaural interaction was found.

These findings were surprising. It was expected that human MOCR responses would be larger when activating the ipsilateral pathway than when activating the contralateral one considering that animal data in cat and guinea pig have shown that more efferent fibers serve the ipsilateral pathway (Liberman and Brown 1986; Brown 1989).

It is unclear why the MOCR needs a contralateral pathway. Redundancy is one possibility, but the asymmetry found in cat is not required for redundancy.

The asymmetry found in cat was also found to be frequency-dependent with more efferent fibers serving the ipsilateral reflex at higher frequencies than at lower ones. It is possible that while there appears to be no functional asymmetry in humans near 1 kHz, the same measurements at higher frequencies would show a difference. A study that looks at ipsilateral vs.

[65] Measurements were made with SFOAEs near 1 kHz, whether ipsilateral/contralateral response differences exist at other frequencies remains to be seen.

contralateral MOCR responses across a wide (e.g. 0.5 to 8 kHz) frequency range is needed.

B. Chapter 3: Time-course of the medial olivocochlear reflex

This chapter quantified the time-course over which the effects of activating the MOCR builds up in the cochlea.

In agreement with previous reports (Sridhar, Liberman et al. 1995; Sridhar, Brown et al. 1997; Kim, Dorn et al. 2001) the reflex was found to act over two time scales (1) 100's of ms and (2) 10's of seconds. Our measurements quantify the faster time scale and show that the buildup is comprised of two time constants—fast ($\tau \sim 70$ ms) and medium ($\tau \sim 330$ ms)—and that the decay is best described by a damped sinusoid.

A second order model could relate the buildup and decay by changing a single model parameter indicating that a single second order process, located somewhere within the reflex loop, may govern the MOCR time-course (on the faster, 100's of ms, time scale).

The demonstration that the fastest MOCR responses were on a 100's of ms time-scale precludes the MOCR from providing any protection from loud impulse sounds such as gunshots.

This study is complete. However, questions like: "Is the time-course different for other stimulus types?" and "Does stimulus bandwidth have an effect on the MOCR time-course?" remain to be investigated.

C. Chapter 4: Efficacy of AM noise for activating the medial olivocochlear reflex

This chapter quantified the efficacy of amplitude modulated (AM) noise relative to unmodulated noise for activating the MOCR. We found AM does not generally increase MOCR response magnitudes over unmodulated wideband stimuli.

Three of 4 subjects did not show an increased response with AM of any rate but 1 subject did show an enhanced response to 100 and 200 Hz AM. It was not determined, however, if the apparent increase was a result of time-dependent variations in the measurements. Consequently, we do not know for certain whether AM modulation can increase responses for some subjects under some conditions. We can say that AM does not appear to *generally* increase MOCR responses.

'AC' and 'DC' components of MOCR responses were also extracted for different modulation rates. DC responses were evident for those modulation rates (2-11 Hz) important in conveying speech information and this level of activation could aid a 'speech perception in noise' role for the MOCR in hearing.

The small number of subject involved in this study and the inconsistent results make it incomplete. To determine with certainty whether AM can enhance DC MOCR responses more experiments involving more subjects are needed. Specifically, AM activators between 50 – 400 Hz, and especially at 100 Hz, should be targeted and an experimental design that interleaves no-AM activators with AM activators thereby minimizing time-dependent variation should be used.

D. Chapter 5: Distribution of medial olivocochlear reflex strengths in normal-hearing humans

This chapter quantified the range and distribution of MOCR strengths in a normal-hearing population (24 subjects). MOCR reflex strength near 1 kHz varied across our normal-hearing subject pool by a factor 7 and the distribution was normal.

Varying degrees of reflex strength within the population could indicate 'tough' and 'tender' ears in the normal population. Prior studies in animals have indicated that the MOCR may help protect the ear from acoustic trauma (Rajan 1995). Furthermore, one study has demonstrated that that a stronger MOCR may provide more protection (Maison and Liberman 2000). This suggests OAE-based tests like this one could identify people susceptible to acoustic trauma. Only one other study has produced normative data on MOCR strength (De Ceulaer, Yperman et al. 2001) and this study had some methodological problems.

The SFOAE-based MOCR measure we used was frequency-dependent. Measurements made at nearby SFOAE frequencies (as close as 40 Hz) in the same subject did not produce similar MOCR measures. This was unexpected. It was presumed that activating the MOCR with wideband noise would uniformly reduce the gain of the cochlea, and it was presumed that this gain reduction was solely responsible for the resultant change in the SFOAE which we used as a measure of reflex strength. The unexpected frequency-dependence could be due to MOCR activation changing micromechanical cellular arrangements, to which SFOAEs are sensitive. Another explanation is that MOCR activation may change the shape of the traveling wave envelope to which SFOAEs are sensitive.

We found that averaging across frequencies (spanning 100 Hz) was able to reduce the frequency-dependent variation (and time-dependent variation)

enough to generate similar measures of MOCR strength within a given subject. Thus, using frequency-averaging, we were able to measure MOCR strength in 24/24 subjects and subsequently quantify the range and distribution of MOCR strengths near 1 kHz across a normal-hearing population.

To transfer this work into the clinic, two steps are needed. First, a correlation between MOCR strength and susceptibility to acoustic trauma needs to be demonstrated in humans. This is a difficult study to do, but it may be possible by investigating TTS in people who are already prone to noise exposure, such as disco junkies and rock-concert aficionados. Second, the speed and reliability of the test must be optimized. TEOAEs may provide a better test because they naturally average across frequency.

II. LESSONS LEARNED ABOUT MEASURING THE MOCR VIA SFOAES

A. Time-dependent variation in the measurements

Time-dependent variations were apparent in repeated measurements. Some of this variation may be due to slowly developing (τ = 10's of seconds) MOCR effect that gradually manifest after many stimulus presentations or other factors such as a subject's arousal or intrinsic cochlear effects that change with time.

B. Frequency-dependent variation in the measurements

Fine scale (within 40 Hz) frequency-dependent variations were apparent in the measurements (see Chapter 5 Appendix A). These variations could not be explained by time-dependent variations. Averaging across 100 Hz reduced the frequency-dependent variation enough to observe underlying subject-dependent MOCR strengths.

C. Implications for experiment design

In designing an experiment to measure MOCR effects using OAEs where the goal is to compare different conditions (e.g. the effect of stimulus bandwidth) those conditions should be measured as close as possible in time and should be interleaved across time to avoid misinterpreting time-dependent variations as differences caused by manipulating the conditions. Similarly, when using SFOAEs, frequency-dependent variations must be considered.

IV. THE ROLE OF THE MOCR IN HEARING

Currently, there is no consensus for the primary role of the MOCR in hearing. There are multiple postulated roles: developmental (Walsh, McGee et al. 1998), protective (Rajan and Johnstone 1983; Reiter and Liberman 1995), dynamic range adjustment (Geisler 1974; Winslow and Sachs 1988), signal detection in noise (Winslow and Sachs 1988; Kawase, Delgutte et al. 1993), and aiding selective attention (Hernandez-Peon 1956; Meric and Collet 1994).

The findings in Chapters 2-5 are consistent with all the postulated roles[66]. A reasonable reply to the question "What is the primary role the MOCR plays in hearing?" is reached by analogy to the pupillary light reflex which constricts the iris in response to bright light. The pupillary light reflex improves acuity (Campbell and Gregory 1960), provides greater dynamic range to the eye, aids in focusing, and protects retinal cells from over-stimulation. It plays many specific roles. Overall, the pupillary light reflex has evolved to help keep our light sensors working optimally across the environmental conditions we face. The same is likely true for the medial olivocochlear reflex and our sound sensors[67].

V. A NEW FUTURE DIRECTION

"Do we have voluntary, involuntary or semi-voluntary control over the MOCR?" For instance, can the machinery of the MOCR be used to reduce auditory input when we wish to direct our attention to visually? (Oatman 1971). The MOCR is a low-level reflex, but it receives input from the inferior colliculus (IC) (Rajan 1990; Vetter, Saldana et al. 1993) and possibly directly from the cortex leaving open the question of what level of control we have over the reflex. We do not yet know if the reflex can be manipulated consciously or if it is affected by emotional states as the pupillary light reflex is known to be. Psychophysical tests in conjunction with MOCR measures have attempted to demonstrate conscious control but the results are inconclusive. The next basic property of the reflex to uncover is, "What level of control do we have on the MOCR?"

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[66] The time scale over which the MOCR acts does not allow for protection from loud impulse sounds such as gunshots.

[67] The hearing system and visual systems face different problems, for instance the hearing system has to deal with hearing the noises we make ourselves and this is also a possible role for the MOCR. A similar reflex loop in the hearing system of a vocalizing fish has been found to have this kind of role (Weeg, Land et al. 2005).

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Biography

EDUCATION

1997-2005	Ph.D. in Health Sciences and Technology, Harvard-MIT Division of Health Sciences and Technology; Massachusetts Institute of Technology/Harvard University, Cambridge, MA.
1991-1995	A.B. in Engineering Sciences with High Honors in Engineering; Dartmouth College. Hanover, NH.

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1995	Phillip R. Jackson Engineering Prize for best engineering product design; safety carton cutter.
1991	Tandy Technology Scholarship; "To the outstanding student in mathematics/science/computer science."
1991	Harvard Book Award; "To the student with outstanding character and scholastic achievement."

PUBLICATIONS

2003	Guinan J.J. Jr., Backus BC, Lilaonitkul W, Aharonson V. J. Medial olivocochlear efferent reflex in humans: otoacoustic emission (OAE) measurement issues and the advantages of stimulus frequency OAEs. Assoc Res Otolaryngol. 2003 Dec;4(4):521-40

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