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Evaluation of Efferent Unmasking Using Cortical Auditory-Evoked Potentials

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Abstract

Purpose. All human beings, regardless of whether they have hearing impairments or not, face difficulties in detecting signals in the presence of background noise. To cope with such situations, people can enhance their performance by either increasing the signal levels or reducing the noise levels, which in turn increases the signal-to-noise ratios (SNRs). SNRs play a crucial role in determining one's speech perception abilities. For instance, if the noise levels are high, individuals may raise their voices or decrease their distance from the source to amplify the signal levels, thereby increasing the SNR. However, in real-life situations, individuals may not be able to control these variables, leading to variations in their ability to detect signals in noise. Such variations may be attributed to differences in the auditory efferent system among individuals. The auditory efferent system can potentially improve SNRs through Medial Olivocochlear Reflex (MOCR)-mediated unmasking, as supported by animal studies. Nevertheless, it is not clear to what extent the efferent system can enhance SNRs in humans. Cortical Auditory Evoked Potentials (CAEPs) can serve as a useful tool to assess the impact of the auditory efferent system on humans, as they are highly sensitive to changes in SNRs.

Methods. Out of the total 50 participants, data from 47 participants were included in the analysis. The primary goal of this study was to investigate the auditory efferent system in humans: aim 1) measures the effect of MOCR activation on CAEPs in response to a tone presented in quiet. A 1-kHz tone at 60 dB SPL was presented to the ipsilateral ear with and without contralateral noise at 60 dB SPL. aim 2) the effect of MOCR activation on CAEPs in response to a tone presented in noise. A 1-kHz tone in noise was presented to the ipsilateral ear at different SNRs (25 dB, 15 dB, and 5 dB). Otoacoustic emissions (OAEs) and tone-detection tests were additionally tested to verify the MOCR effect.

Results. In Aim 1, it was expected that the MOCR effect would decrease SNR, resulting in increased latency and decrease inter-amplitude. However, no noticeable changes in latency and inter-amplitude were observed as a result of the MOCR effect. In Aim 2, it was expected that the MOCR effect would enhance SNR, resulting in decreased latency and increased inter-amplitude. The unmasking effect on latency and inter-amplitude was observed only at specific SNR levels at 5 dB and 15 dB SNR. Furthermore, the correlation between the shift in OAE level and tone-detection level was found to be unrelated in Aim 1. However, in Aim 2, a significant correlation was observed between these shifts at a specific SNR, specifically at 5 dB or 15 dB SNR.

Conclusions. In aim 1 (MOCR effect in a quiet environment), the activation of the MOCR does not significantly affect LLR latency and inter-amplitude. One possible factor that influences these results is the duration of the measurement session, as it may reduce the MOCR effect. Another possibility is that the reduction in cochlear output caused by MOCR activation may be compensated for by central gain. In aim 2 (MOCR effect in noise environment), LLR latency decreases during MOCR activation at 5- and 15-dB SNR, indicating that the efferent system enhances SNR through the MOCR-mediated unmasking effect at the neural level. Specifically, the unmasking effect increases sensitivity to a specific SNR. However, we were unable to identify a relationship between MOCR metrics, pre-neural assay, and behavioral assay. The lack of association in the MOCR analysis may be attributed to the use of different stimuli, diminished MOCR effect over time, and the introduction of high artifacts.

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Evaluation of Efferent Unmasking Using Cortical Auditory-Evoked Potentials

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DEDICATION

This dissertation is an expression of my heartfelt gratitude to all the individuals who provided invaluable assistance throughout my doctoral degree. Firstly, I would like to extend my deepest appreciation to my wife, Shullee, whose unwavering support and encouragement have been a constant source of strength. Additionally, I am immensely grateful to my advisor, Dr. Lewis, for imparting invaluable knowledge and serving as both a mentor and a friend. I would also like to thank my family, whose prayers and unwavering support have been instrumental in my journey. Completing my doctoral course was far from an easy feat, but it is through the tremendous support of these exceptional individuals that I have achieved this milestone. As I embark on this new chapter, I am confident that I will emerge as a proficient and compassionate researcher in the field of audiology, eager to make a positive impact.

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Finally, I would like to express my heartfelt gratitude to my friends, family, and my beloved wife. Their unwavering presence by my side, constant support, and fervent prayers have played an indispensable role in shaping my journey. I firmly believe that without their heartfelt prayers, I would not have achieved the remarkable position I find myself in today.

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PREFACE

The body of this dissertation is structured to provide readers with a clear and logical progression. Firstly, we present the rationale for selecting the research topic, objectives, and hypotheses, along with an overview of the relevant literature. Each objective is dedicated to its own chapter. Chapter 1 comprises a literature review that aims to develop a comprehensive understanding of the research. In Chapter 2, we introduce the role and measurement methods of the auditory efferent system in both humans and animals. Chapter 3 provides an overall overview of the study and explains the necessity of conducting the research. In Chapter 4, we present the first research goal, along with the corresponding research methodology and results. Chapter 5 focuses on explaining the second research goal, research methodology, and results. Finally, in concluding Chapter 6, we synthesize all the research elements, including limitations and future works, and offer our final thoughts on the findings and their significance.

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ABSTRACT

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LIST OF ABBREVIATIONS

ABR	Auditory Brainstem Response
Ach	Acetylcholine
AEP	Auditory Evoked Potentials
ANL	Acceptable Noise Level
CAEP	Cortical Auditory Evoked Potentials
CAP	Compound Action Potentials
CEOAE	Click-Evoked Otoacoustic Emissions
CF	Characteristic Frequency
CGRP	Calcitonin Gene-Related Peptide
CN	Cochlear Nucleus
CM	Cochlear Microphonic
DPOAE	Distortion Product Otoacoustic Emissions
GABA	Gamma-Aminobutyric Acid
IC	Inferior Colliculus
IHC	Inner Hair Cell
LL	Lateral Lemniscus
LLR	Late Latency Responses
LOC	Lateral Olivocochlear
LOCR	Lateral Olivocochlear Reflex
LSO	Lateral Superior olive
MEMR	Middle Ear Muscle Reflexes
MGB	Medial Geniculate Body
MLR	Middle Latency Response
MOC	Medial Olivocochlear
MOCR	Medial Olivocochlear Reflex
NIHL	Noise Induced Hearing Loss
OAE	Otoacoustic Emissions
OCB	Olivocochlear Bundle
OHC	Outer Hair Cells
OSHA	Occupational Safety and Health Administration
PTS	Permanent Threshold Shifts
PVCN	Posterior Ventrual Cochlear Nucleus
RMS	Root Mean Square
SD	Standard Deviation
SNR	Signal-to-Noise Ratios
SFOAE	Stimulus Frequency Otoacoustic Emissions
SOAE	Spontaneous Otoacoustic Emissions
SOC	Superior Olivary Complex
TEOAE	Transient Evoked Otoacoustic Emissions

CHAPTER 1. INTRODUCTION

Significance of Research

Signal-to-noise ratios (SNRs) have a significant impact on speech perception abilities. While animal studies have provided evidence showing the potential of medial olivocochlear reflex (MOCR) mediated unmasking to enhance SNR, it remains uncertain whether this occurs in humans. Therefore, the aim of this study was to evaluate the potential role of the human auditory efferent system, particularly the medial olivocochlear branch, in enhancing neural encoding of signals in noise. Cortical auditory evoked potentials (CAEPs) were the primary tool by which the MOCR was evaluated as they are sensitive to SNRs (Billings et al., 2009).

Chapter 1 provides an overview of the anatomy and physiology of the auditory efferent system, including the lateral olivocochlear reflex (LOCR) and the MOCR. This helps to understand the pathways of the overall auditory efferent system. Chapter 2 discusses the role of the auditory efferent system in hearing, based on animal studies conducted over the past few decades. Specific focus is on the predicted role of the MOCR in protecting the ear from acoustic injuries and facilitating signal detection in noise through a concept known as unmasking. Additionally, this chapter provides information about the MOCR in humans, including its anatomy, function, and measurement methods. Specific focus is on evidence for and against the hypothesized MOCR-mediated unmasking effect, and the potential utility afforded by CAEPs in evaluation of unmasking. In Chapter 3, the research related to MOCR and CAEPs is discussed, accompanied by an explanation of the importance of the conducted research. This chapter also presents the research questions, rationale, and hypotheses for this dissertation research. This work focuses on two main research questions: 1) Do CAEPs show evidence of SNR reduction during MOCR activation when listening in quiet? 2) Do CAEPs show evidence of SNR improvement during MOCR activation when listening in noise? Chapter 4 details the experimental design and results for the first research question. In Chapter 5, the experimental design and results for the second research question are detailed. Chapter 6 provides a summary of the findings and a discussion of their implications.

Exploring the relationship between CAEP and the efferent system, specifically the MOCR-mediated unmasking effect, can enhance our understanding of the role of the human efferent system. Additionally, these findings may shed light on why some individuals have more difficulty detecting signals in noise than others, as they may exhibit different unmasking effects. As a result, this study could contribute to the development of clinical tools for evaluating the MOCR using CAEPs.

Anatomy and Physiology of the Auditory Efferent System

The Efferent System

The descending system, also known as the efferent system, refers to neural pathways that originate from the brain and/or brainstem, and extend to peripheral body structures including muscles and sensory organs. The auditory efferent fibers originate in the auditory cortex (layers IV and V), descend to the medial geniculate body (MGB) through the internal capsule, then continue to the inferior colliculus (IC), lateral lemniscus (LL), superior olivary complex (SOC), and the cochlea. Olivocochlear efferent fibers originate from the left and right SOC. They enter the cochlea via the cochlear nerve (VIIIth cranial nerve). The olivocochlear efferent fibers were first identified by Rasmussen (1946).

The efferent olivocochlear system has two segments differentiated by the location of the cell bodies and their termination: the lateral olivocochlear (LOC) bundle, which is thought to synapse on the Type I afferents of the cochlear nerve at the inner-hair cell (IHC) synapse (Simmons, 2002), and the medial olivocochlear (MOC) bundle (Warr & Guinan, 1979), which terminate on the outer hair cells (OHCs). The MOC and LOC neurons are distributed differently among species in terms of numbers. Cats are thought to have approximately 860 LOC neurons and 500 MOC neurons (Arnesen & Osen, 1984). For adult humans, it is thought that there are approximately 1,000 LOC fibers and between 300 – 400 MOC fibers (Arnesen, 1984).

Both the MOC and LOC bundles convey signals to the periphery through obligatory mechanisms. Apart from their anatomical differences, there are also functional differences. The MOC neurons are responsible for the MOCR, which is thought to reduce cochlear amplification within the cochlea, results in protection ear from acoustic trauma and aid in speech perception in noise. Little is known about the role of feedback from the LOC bundle.

Another efferent pathway is responsible for what is known as the acoustic reflex, or middle ear muscle reflexes (MEMR). The MEMR is mediated through two muscles the stapedius muscle and tensor tympani muscle. The stapedius muscle receives innervation from the facial nerve (VII), whereas the trigeminal nerve (V) provides innervation to the tensor tympani muscle. The stapedius muscle is thought to be the primary driver of the MEMR (Stach et al., 1984). The MEMR is activated in response to high level sound: Sound information is transmitted from the inner ear to the cochlear nucleus (CN) through the VIII nerve, and then to the SOC. Descending neurons synapse at the facial nerve nucleus and information is then transmitted to the stapedius muscle through the facial nerve (cranial nerve VII). This results in the contraction of the stapedius muscle.

Both the MOCR and MEMR reduce sound transmission to the ear. However, they do so through different mechanisms. The MOCR reduces cochlear amplification resulting in reduced input to the cochlear nerve, whereas the MEMR increased middle ear

impedance resulting in reduced input to the cochlea. The focus of the present study is on the MOCR.

The Lateral Olivocochlear Reflex (LOCR)

LOC neurons beneath the inner hair cells are affected from both sides as the afferent posterior ventral cochlear nucleus (PVCN) activates the lateral superior olive (LSO). Although some studies have suggested that the LOC neurons can be activated by sound (Thompson & Thompson, 1991), subsequent research by Guinan (2014) has shown that there is limited support for sound-evoked activation of the LOC neurons. Despite uncertainty in how they are activated, there is evidence to suggest that the LOC neurons play a role in protecting the ear from acoustic injury and age-related auditory processes (Liberman et al., 2014). However, compared to the MOC bundle, the functional role of the LOC bundle is less well-known (Guinan, 2014; Liberman et al., 2014). LOC neurons produce several neurotransmitters, such as Acetylcholine (Ach), Gamma-aminobutyric acid (GABA), calcitonin gene-related peptide (CGRP), dopamine, that exhibit both excitatory and inhibitory properties. Compared to MOC neurons, LOC neurons are smaller and unmyelinated, which presents challenges in measuring and analyzing their function due to difficulties in electrical stimulation. As a result, the precise function of LOC neurons remains unclear, emphasizing the need for further research to gain a comprehensive understanding of their mechanisms and effects.

The Medial Olivocochlear Reflex (MOCR)

Contrary to the LOC efferent branch, there have been many studies examining the anatomy, physiology, and function of the MOC efferent branch. The MOC neurons originate in the medial olivary complex and synapse with OHCs (Liberman & Brown, 1986; Brown, 1987). MOC neurons are thick and myelinated. The number of MOC fibers connected to OHCs varies depending on the species. A single MOC fiber may contact 23 – 84 OHCs in cats (Liberman & Brown, 1986) and 14 – 69 OHCs in guinea pigs (Brown, 2014). Humans are also predicted to have MOC fibers connected to several OHCs, although there is evidence for reduced innervation compared to lower mammals (Liberman & Liberman, 2019). The density of MOC neurons in the cochlea varies, with the highest density found in the upper basal turn (4 kHz regions) of the cochlea, as reported by Liberman and Liberman (2019).

There are two functions associated with MOC feedback to the cochlea through the MOCR: 1) protecting the ears from acoustic injuries (Handrock & Zeisberg, 1982; Rajan & Johnstone, 1983; Rajan 1988; Reiter & Liberman, 1995; Reiter & Liberman 1995; Attanasio et al., 1999; Maison & Liberman, 2000; Luebke & Foster, 2002; Kujawa & Liberman, 2009; Maison et al., 2013; Luebke et al., 2014; Liberman et al., 2014; Boero et al., 2018) , 2) improving SNRs to facilitate signal detection in noise (Winslow and Sachs, 1987; Kawase et al., 1993). The MOC neurons are activated by acoustic stimulation and may be modulated by attention (Delano et al., 2007; Bowen et al., 2020).

Numerous studies have shown that MOC feedback to the OHCs reduces cochlear amplification by inhibiting OHC electromotility (Siegel & Kim, 1982; Dallos et al., 1997; Guinan & Gifford, 1988; Wersinger & Fuchs, 2011; Guinan, 2018). Specifically, when sound enters the ear, the basilar membrane vibrates and this movement is amplified by the effect of OHC electromotility. Electromotility refers to the change in the length of the OHC upon transduction events (depolarization and hyperpolarization) and, by extension, intra-cellular voltage changes (Brownell et al., 1985; Santos-Sacchi & Dilger, 1988). The cochlear amplification provided by the OHCs is driven by the motor protein prestin (Zheng et al., 2000; Dallos et al., 2008). For instance, Liberman et al. (2002) demonstrated that prestin-KO mouse, which eliminate the motor protein responsible for electromotility, lacked OHC motility, resulting in elevated hearing thresholds presumably due to reduced OHC amplification. Activation of the MOC neurons reduces the vibration of the basilar membrane (Murugasu & Russell, 1996; Cooper & Guinan, 2006) through communication with the OHC by the neurotransmitter Ach (Elgoyhen et al., 2001). Ach causes calcium channels along the basal-lateral surface of the OHC to open and calcium to enter the OHC. This causes the opening of calcium-activated potassium channels and potassium outflow through the potassium channels. As a result, the OHC undergoes hyperpolarization (Fuchs, 2002), leading to a decrease in basilar membrane vibration (Cooper & Guinan, 2006). This decrease ultimately lowers the sensitivity and frequency selectivity of the cochlea.

Figure 1-1 illustrates the effect of MOCR activation on basilar membrane displacement (dynes/cm^2) across input sound levels, measured at a single, fixed location. The blue line represents the displacement of the basilar membrane when the MOCR is inactive. The **Figure 1-1** employed the equation from Winslow and Sachs (1988) and utilized input sound levels to observe the basilar membrane displacement. In this model, the basilar membrane displacement grows linearly with input sound level until it reaches a threshold value of 35 dB SPL. Beyond this threshold, the displacement grows compressively due to reduced OHC amplification and a basal shift in vibration (not shown). Upon MOCR activation, the threshold shifts from 35 to 45 dB SPL due to a decrease in basilar membrane displacement caused by reduced cochlear amplification. As a result of reduced basilar membrane vibration upon MOCR activation, the inner hair cell response is also reduced (Brown & Nuttall, 1984), as is the firing rate of the Type I afferent auditory nerve fibers that synapse on the inner hair cells (Gifford & Guinan, 1987).

The MOCR is mediated through two pathways: the crossed (ipsilateral reflex) and the uncrossed (contralateral reflex) pathways (Liberman & Brown, 1986). For the ipsilateral MOCR, sound energy arriving in the ipsilateral ear travels to the ipsilateral cochlear nucleus via the VIIIth nerve, and neurons of the ipsilateral cochlear nucleus cross the brainstem and synapse on the MOC neurons of the contralateral side. The MOC neurons then cross back to the ipsilateral cochlea through the crossed olivocochlear bundle. For the contralateral MOCR, sound energy arriving in the contralateral ear travels to the contralateral cochlear nucleus via the VIIIth nerve, and neurons of the cochlear nucleus cross the brainstem and synapse on the MOC neurons on the ipsilateral side. The MOC neurons connect to the ipsilateral cochlea through the uncrossed olivocochlear

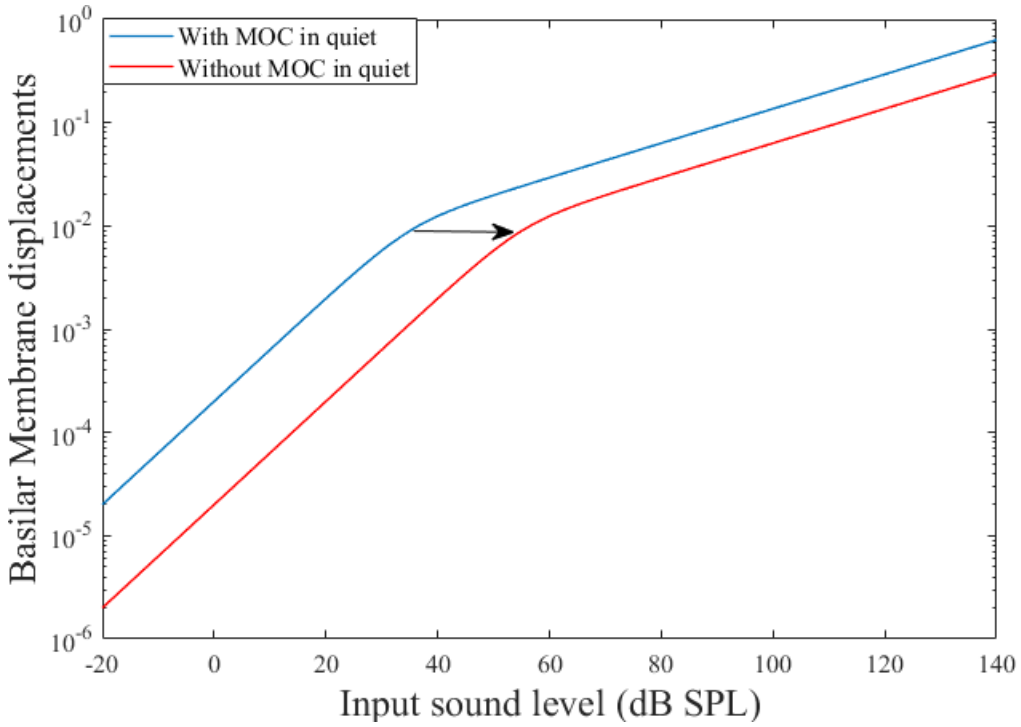

Figure 1-1. Basilar membrane displacements.
The blue line represents the basilar membrane displacement without MOCR activation, whereas the red line represents the basilar membrane displacement with MOCR activation. The arrow highlights the shift of the basilar membrane displacements from no-MOCR activation to MOCR activation.

bundle (de Venecia et al., 2005). In small animals, the number of ipsilateral MOC fibers is approximately three times higher than contralateral fibers (Warr, 1992). According to Guinan (2006), in the primate model, the strength of ipsilateral and contralateral MOC reflexes shows a nearly equal ratio of approximately 1-to-1. Therefore, there may be no significant difference in strength between ipsilateral and contralateral MOC reflexes; however, human studies suggest a stronger ipsilateral reflex (Liaonitkul & Guinan, 2012).

When the MOCR is activated through these pathways, the tuning curves of the MOC fibers show narrow tips, and each individual MOC fiber stimulates the cochlea with its respective best frequencies (Robertson 1984; Liberman & Brown 1986; Brown, 1989). This results in frequency-specific feedback to the corresponding location responsible for each frequency. Consequently, cochlear regions innervated by efferent neurons are closely situated to afferent fibers of the same characteristic frequency (CF) (Liberman & Brown, 1986). Hence, this suggests that the activation of the MOCR can influence the specific frequency of the cochlear regions.

The MOCR operates on fast and slow time scales. The fast effect corresponds to inhibition of basilar membrane motion and a reduction in auditory nerve activity within approximately 100 milliseconds of sound onset (Cooper & Guinan, 2003; Backus & Guinan, 2006). The slow effect occurs on a much longer time scale (i.e., 10-100 seconds) (Cooper & Guinan, 2003), and is thought to be related to slow calcium release and potential stiffness changes in the OHCs (Cooper & Guinan, 2003, Dallos et al., 1997). Both fast and slow MOCR effects reduce the basilar membrane response to sound (Cooper & Guinan, 2003), but they have different effects on the basilar membrane phase. The fast effect results in a phase lead, while the slow effect results in a phase lag (Cooper & Guinan, 2003).

In summary, MOC fibers synapse on OHCs, acting to reduce cochlear amplification (Guinan, 1996; Fuchs, 2002; Cooper & Guinan, 2006). The significance of this action is not well understood in humans. However, animal work has led to the hypothesis that these effects serve two distinct purposes: protecting against acoustic trauma caused by noise exposure and assisting in signal detection in noisy environments.

CHAPTER 2. ROLE OF THE ADUTORY EFFERENT SYSTEM IN HEARING

Animal Research

Protection Against Acoustic Trauma

High levels of noise exposure can cause noise-induced hearing loss (Saunders et al., 1985). Over the past few decades, animal studies have aimed to investigate whether the MOCR helps protect hearing during high noise exposures. Evidence from animal studies indicates that the MOCR plays a vital role in protecting the ear from potential acoustic trauma (Handrock & Zeisberg, 1982; Cody & Johnstone, 1982; Rajan & Johnstone, 1983; Reiter & Liberman 1995; Attanasio et al. 1999; Maison & Liberman, 2000; Luebke & Foster, 2002; Kujawa & Liberman, 2009; Maison et al., 2013; Luebke et al., 2014; Liberman et al., 2014; Boero et al., 2018).

Handrock and Zeisberg (1982) conducted an experiment where they exposed guinea pigs to noise and observed changes in threshold by measuring compound action potentials (CAP) amplitude. They found that the group with several olivocochlear bundle (OCB) excisions experienced a greater degree of permanent hearing loss compared to the control group. Therefore, this study provides evidence supporting the role of the auditory efferent system in protecting hearing from noise. Cody and Johnstone (1982) demonstrated protection of the ears from acoustic injuries in guinea pigs through contralateral acoustic stimulation, which activates the contralateral MOCR. Similarly, Attanasio et al. (1999) employed animal subjects to assess threshold shifts in both a control group and a group with OCB sectioning, following exposure to continuous noise (4 KHz at 85 dB SPL) for 6 hours per day over a span of 10 days. Initially, a similar pattern of threshold shift was observed in both groups for the first 2 days. However, starting from the 3rd day, the animals with OCB sectioning exhibited a larger threshold shift of 50 dB. By the 5th day, a significant 30 dB threshold difference compared to the control group was evident. This study suggests a role of these neurons in preserving hearing. Maison and Liberman (2000) conducted a study on noise-induced hearing changes in animals as they relate to the amount of MOCR feedback. Animals were first classified into two groups based on the strength of their MOCR: a “tender ear” group (i.e., weak MOCR strength) and a “tough ear” group (i.e., strong MOCR strength). Threshold changes were measured in animals post exposure to various noise bandwidths at 109 dB SPL for 4 hours. One week after noise exposure, hearing sensitivity was evaluated using distortion product otoacoustic emissions (DPOAE) and CAP. The results demonstrated that animals with a strong MOCR exhibited a threshold shift of up to 20 dB, whereas those with a weak MOCR experienced a shift ranging from 35 dB to 70 dB. This study demonstrates that the stronger the MOC reflex, the greater the resistance to permanent thresholds shifts (PTS).

Aside from protecting the OHCs, MOCR feedback may also protect other inner ear structures including the inner hair cells and afferent neurons. Cochlear

synaptopathy/neuropathy refers to a condition where permanent damage has occurred to the inner ear but the damage does not result in a PTS (Kujawa & Liberman, 2009; Jensen et al., 2015). Cochlear neuropathy is thought to have a primary effect on signal detection and discrimination in noise (Furman et al., 2013). Recently, Maison and colleagues (2013) conducted a study on mice exposed to moderate noise levels (84 dB SPL). They found that efferent feedback could alleviate cochlear neuropathy. A study conducted by Boero et al. (2018) provided evidence that MOC feedback plays a protective role against inner ear hearing loss, as observed in a group where the olivocochlear bundle was eliminated. In the intact condition, a threshold shift was observed following noise exposure, but the majority of the hearing was subsequently restored. Conversely, in the group lacking an intact olivocochlear bundle, some of the hearing thresholds recover, but not all hearing sensitivity.

Animal studies provide evidence that the MOCR plays a protective function in the auditory system. This role is challenging to examine in human research due to ethical factors that preclude exposing humans to hazardous noise levels and durations. Excessive noise levels and long-term noise exposure, as utilized in animal research, can result in permanent, noise-induced hearing loss (NIHL) in humans. According to the Occupational Safety and Health Administration (OSHA), only eight hours of exposure to 90 dBA noise levels is allowed, and the permitted exposure time is halved for every 5 dB increase. Due to restrictions on the use of noise that may cause hearing loss, human studies typically analyze the effects of the MOCR by activating or deactivating it using moderate noise levels. Consequently, such limited noise exposures likely restrict the amount of information that can be gained concerning the protective effects of the MOCR in humans.

Detection of Signals in Noise

The MOCR may also aid in the detection of signals in noise by enhancing the SNR through a process known as “unmasking”. Animal studies have provided the theoretical basis for MOCR-mediated unmasking (Winslow & Sachs, 1988; Dolan & Nuttall, 1988; Kawase et al., 1993), demonstrating the auditory nerve response to transient signals in noise is enhanced upon MOCR activation. Specifically, the MOCR increases the neuron’s response to the signal and decreases the neuron’s response to the noise.

Figure 2-1 illustrates MOCR unmasking by way of comparing simulated type I afferent neuron rate-level functions to signals in quiet (left) and noise (right), both with and without MOCR activation. These simulations are based on Winslow and Sachs (1988) auditory model. The left panel depicts the impact of MOCR activation on the rate-level function of a neuron in a quiet environment, using a tone range spanning from -20 dB to 140 dB SPL, as shown in the rate-level function demonstrated by Winslow and Sachs (1988). Activation of the MOCR leads to a rightward shift of the rate-level function by 20 dB (in this example; the actual shift depends on the amount of MOCR feedback), which is attributed to reduced cochlear amplification. In the right panel, the response of the neuron is masked by 30 dB SPL noise, as seen by the red dashed line. Masking of the neuron’s responses occurs through three phenomena. First, the noise

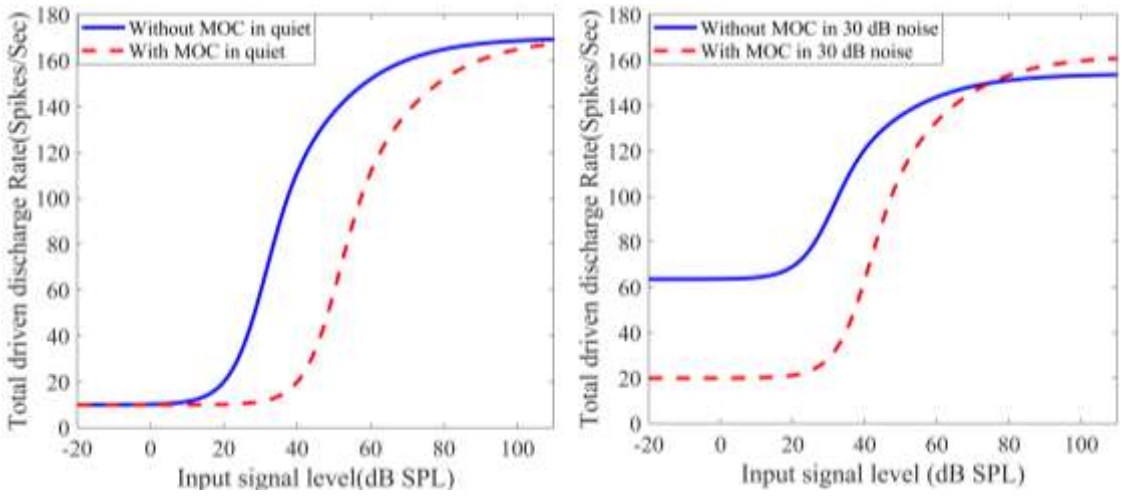

Figure 2-1. Schematic of the mid-spontaneous fiber rate-level function in quiet and noise with and without MOCR.

The red dashed line shows the neuron's rate-level function response to a tone in quiet (left) and noise (right), with MOCR activation. The blue dashed line shows the neuron's rate-level function response to a tone in quiet (left) without MOCR activation and noise (right) without MOCR activation.

increases the firing rate of the auditory neuron; this is referred to as the “line busy” effect (Delgutte, 1990). Second, due to two-tone suppression within the cochlea, the noise decreases the neuron's firing rate to input levels above those of the noise (Pang & Guinan, 1997). Third, the noise reduces the auditory neuron’s firing rate at high input levels, as a result of adaptation. The IHC neurotransmitter depletion is a contributing factor to adaptation (Boero et al., 2021). As a result, noise reduces the dynamic range of the auditory nerve firing rate. Additionally, the difference in the neuron’s response between sounds above the noise level and the noise level itself is reduced. As a result, detection of signals is negatively affected by noise masking.

However, with MOC activation (as seen by the blue solid line), the noise masking is reduced. This is evidence of MOCR-mediated unmasking. The MOCR inhibits the neuron’s response to the background noise, thereby restoring the neuron’s dynamic range and enhancing the neuron’s response to sounds above the background noise. Theoretically, this action has the potential to improve an individual's ability to detect signals in noise.

Evidence of MOCR unmasking comes from a number of studies. Kawase and Liberman (1993) report evidence of MOCR unmasking measured in single auditory-nerve fibers responding to a tone-burst in noise using cats. In this study, they compared MOCR activation in a quiet environment with CAP in response to MOC activation in noise. In quiet environments, the waveforms were smaller when contralateral noise was present and larger in the presence of noise. In the presence of noise, the CAP amplitude showed improvement when the contralateral noise was presented compared to when the masker was presented to the ipsilateral ear only. One interesting finding is that no significant differences were observed in these changes at low tone levels. However, at a specific tone level (starting from 40 dB SPL in the study), a notable difference in CAP amplitude was observed.

Nieder and Nieder (1970) studied unmasking in guinea pig using the CAP. The neural response to a signal in noise was measured under two conditions – MOCR active and inactive (i.e., with and without contralateral noise). When noise was introduced on the ipsilateral side of the signal, resulting in energetic masking, the CAP decreased in amplitude. However, when contralateral noise was also presented to elicit the MOCR, the CAP increased in amplitude. As demonstrated in these animal studies, the MOCR results in suppression of background noise while enhancing the response of neuron to the signal.

Human Research

Comparison of MOCR Anatomy Between Humans and Other Mammals

Humans and other mammals have similar olivocochlear systems. However, compared to other mammals, the influence of the MOC efferent on hearing may be diminished in humans (Liberman & Gao, 1995Liberman et al., 2014; Liberman & Liberman, 2019). For example, a cat has 500 MOC fibers (Arnesen & Osen, 1984) while a human has 360 MOC fibers (Arnesen, 1984). The distribution of the MOC fibers also differs across the species. For example, in humans, the highest density occurs approximately 40% from the cochlear base, compared to 50% from the base in mouse, 20% from the base in rhesus monkey, and 30% from the base in guinea pig (Liberman & Liberman, 2019. Locations with higher MOC innervation density are associated with a stronger MOCR response (Liberman & Liberman, 2019). Differences in the number of MOCs linked to OHCs vary across species, as observed by Liberman & Liberman in 2019. While most species exhibit an approximate one-to-one connection ratio, there are variations. For instance, rhesus shows a connection of 15 fibers to 15 OHC, the guinea pig demonstrates 13 fibers connected to 14 OHC, and the mouse displays 17 fibers connected to 16 OHC. In contrast, humans have a lower ratio of 8 fibers connected to 13 OHCs. It is crucial to acknowledge that the distribution of MOCs can vary across the frequency, particularly when considering the highly dense distribution.

Measurement of the MOCR in Humans

Various techniques are available to measure the MOCR in humans. However, these methods are all limited compared to methods appropriate for animal work. In animal studies, the MOCR can be directly measured through invasive techniques (e.g., by inserting a needle electrode into the auditory nerve). Such approaches are not appropriate for humans and measurements rely on either indirect objective assays or subjective behavioral assays, as discussed below.

Otoacoustic emissions (OAEs)

The typical way to measure the MOCR in humans is by otoacoustic emissions (OAEs). OAEs provide a simple, efficient, and non-invasive measure of OHC function. David Kemp first reported the existence of OAEs (Kemp, 1978). In an ear with healthy OHCs, using a miniature loudspeaker and microphone situated in the ear canal, he measured a cochlear response evoked by an external acoustic stimulus. He called this response an “otoacoustic emission”. OAEs are primarily classified into two types: spontaneous and evoked. Spontaneous otoacoustic emissions (SOAEs) occur without external sound and are found in less than 40% of individuals with normal hearing (Kuroda, 2007). Transient-evoked otoacoustic emissions (TEOAEs), DPOAEs, and stimulus-frequency otoacoustic emissions (SFOAEs), on the other hand, are evoked by acoustic stimuli. Each of these types of OAE can be used to assess cochlear health and

are used in newborn hearing screening programs (Kemp, 2002). TEOAEs are evoked by brief sounds like clicks and generated through a mechanism known as linear coherent reflection (Shera & Guinan, 1999). DPOAEs are evoked by the simultaneous presentation of two tones at different frequencies. These frequencies interact in the cochlea and generate a distortion product through a combination of intermodulation distortion and linear coherent reflection (Shera & Guinan, 1999). SFOAEs are evoked by single tones and generated through linear coherent reflection (Shera & Guinan, 1999).

Unlike other subjective tests that primarily measure individual thresholds, OAEs are an objective and measurable test. However, it is important to note that OAEs cannot be measured when the hearing threshold surpasses 20 to 30 dB HL (Harris & Probst, 1991). Additionally, the generation of OAEs requires the OHC being in a healthy state. Therefore, if OHCs are damaged, OAEs are typically absent.

OAEs are affected by the MOCR because they are a byproduct of OHC amplification, which is reduced upon MOCR activation. OAE-based measurements of the MOCR typically entail comparing OAE characteristics (magnitude and phase) between MOCR conditions: MOCR active and MOCR inactive. In OAE assays of the MOCR, activation of the MOCR occurs via noise presented either ipsilaterally, contralaterally, or bilaterally. Lilaonitkul and Guinan (2009) reported no significant difference in the ratio of ipsilateral and contralateral MOC effects. However, the largest MOC effect can be expected when bilateral acoustic stimulation is employed, as indicated by studies conducted by Guinan et al. (2003) and Lilaonitkul and Guinan (2009).

MOCR strength is estimated by calculating the magnitude and phase differences in the OAE between MOCR conditions. In most cases, MOCR activation causes an advance in the OAE phase (Giraud et al., 1996; Deeter et al., 2009; Goodman et al., 2021) and reduction of the magnitude (Berlin et al., 1993; Moulin et al., 1993; Hood et al., 1996; Guinan et al., 2003; Liaonitkul & Guinan, 2009; Deeter et al., 2009; Zhao et al., 2015). Larger MOCR-induced OAE magnitude and phase shifts are thought to correspond to a stronger MOCR.

OAE-based MOCR studies have been useful in revealing numerous aspects of how the MOCR works. Lilaonitukul and Guinan (2009) and others have demonstrated that MOCR strength is highest when activation occurs by noise with a broad bandwidth. This suggests the MOCR integrates sound energy across the entire cochlea (Maison et al., 2000; Velenovsky & Glattke, 2002; Lilaonitkul & Guinan, 2009; Lee & Lewis, 2023). The MOCR is also shown to be sensitive to the level (or magnitude) of the activator. Specifically, higher noise levels result in larger magnitude and phase changes (Guinan et al., 2003; Backus & Guinan, 2006; Mertes, 2018). OAE-based studies have also revealed the time course of the efferent system. In James et al.'s (2002) study, suppression and latencies of DPOAE were observed using contralateral acoustic stimulation and found that the average delay for suppression was 43 ms. In the study conducted by Backus and Guinan (2006), the researchers examined the time-course of MOCR-induced contraction when stimulated with SFOAEs. They selected 9 ears as targets for activating the MOCR and observed that each exhibited different temporal dynamic range. In general, onset and

offset occurred approximately 25-ms post activator onset and offset. Zhao and Dhar (2011) also investigated the time-course of MOCR using contralateral acoustic stimulation, only in SOAEs. The introduction of contralateral acoustic stimulation resulted in a reduction in magnitude, with a greater reduction observed at higher contralateral acoustic stimulation levels. The study revealed cycles of onset, adaptation, offset, and recovery following the onset of contralateral acoustic stimulation.

Measurements based on OAE have revealed measurements of MOCR tuning, which is evidence of frequency specificity (Veuillet et al., 1991 (TEOAE); Chéry-Croze et al., 1993 (DPOAE); Lilaonitkul & Guinan, 2012 (SFOAE); Zhao & Dhar, 2011 (SOAE)). The MOC effect may exhibit slight variations depending on the site of MOC activation. Liaonitkul and Guinan (2012) reported that the largest MOC effect occurred at the activation frequency during ipsilateral activation, while the greatest MOC effect was observed at a frequency 0.5 octave lower than the corresponding frequency during bilateral activation. These findings imply that the MOC fiber is connected to the OHC at or near that frequency place along the basilar membrane, indicating a frequency specificity within or close to the induced frequency.

Although OAEs are useful tools to evaluate the efferent system in both animals and humans, they do have limitations. For example, OAE cannot be measured in subjects with hearing loss. Therefore, measuring MOCR using OAE is primarily restricted to individuals with normal hearing. Additionally, as OAEs are pre-neural responses, they do not reveal how MOCR-induced changes in the cochlea are represented at the neural level. Unmasking is thought to occur at the neural level, therefore, OAEs can provide only limited information on MOCR function.

Compound action potentials (CAPs)

Auditory evoked potentials (AEPs) reflect electrical activity resulting from neural conduction of sound within the auditory system. They allow investigation of both the peripheral and central auditory systems. Among these measurements, the CAP offers an additional means to evaluate the MOCR. The CAP is associated with the simultaneous firing of many type I afferent auditory nerve fibers in response to sound. Aside from providing a neural assay of the MOCR, another benefit of CAP-based assays is that the effects tend to be larger than those measured using OAEs (Chabert et al., 2002; Smith et al., 2017).

Folsom and Owsley (1987) investigated the effect of MOCR activation on CAP. They found that MOCR activation (via contralateral noise) led to a reduction in CAP amplitude. Their study reported approximately a 15-22% decrease in CAP amplitude in response to clicks. Smith and colleagues (2017) employed CAP to investigate the amplitude changes during MOCR activation. Their findings demonstrated a consistent reduction in amplitude across all click levels when MOCR was activated. Notably, when comparing the use of chirp and click stimuli, a more pronounced effect was observed at lower levels with chirp stimulation. These studies demonstrate that MOCR activation affects not only the pre-neural response but also the neural response. Lichtenhan et al.

(2016) used contralateral acoustic stimulation to measure CAP amplitude and examine the effects of MOCR activation. The results demonstrated a reduction in CAP amplitude of 1.98 dB.

The previously mentioned studies have only investigated the effects of activating MOCR for a signal in quiet. These studies demonstrate a reduced CAP, consistent with reduced cochlear output upon MOCR activation. Several other studies have explored the effect of MOCR activation on signals in both quiet and noisy environments. As discussed in the animal section of this chapter, Nieder and Nieder (1970) found that the magnitude of the CAP evoked by a click in quite decreased upon MOCR activation. However, for a click in noise, the magnitude of the CAP increased with MOCR activation. Kawase and Tasaka (1995) report similar findings humans.

Behavioral testing

Two main approaches to evaluating the MOCR using behavioral means include tone-detection tasks (Micheyl & Collect, 1996; Micheyl et al., 1997) and speech detection tasks (Giraud et al., 1997; Kumar & Vanaja, 2004; de Boer & Thornton, 2008; de Boer et al. al., 2012; Mertes et al., 2018). The role of the MOC reflex can be examined by analyzing the OAE and behavioral studies (Micheyl & Collet, 1996; Bhagat & Carter, 2010; Karunarathne et al., 2018). Other various psychoacoustic tasks have also been used including contralateral masking that involves the activation of the medial olivocochlear reflex (MOCR), which reduces cochlear amplification and subsequently increases the threshold during behavioral tests. By comparing the increased behavioral threshold with CAEPs, the central gain can be deduced. MOCR activation leads to reduced cochlear and neural activity in quiet environments (Guinan & Gifford, 1988). On the other hand, simultaneous masking is expected to enhance speech perception performance through its unmasking effect. This effect enhances the encoding of signals in noisy environments, as shown in studies by Winslow and Sachs (1987), Kawase et al. (1993), and Kawase and Liberman (1993). These MOCR-mediated unmasking effects, observed in animal studies, have also been observed in human behavioral studies.

Cortical auditory evoked potentials (CAEPs)

CAEPs offer a non-invasive approach to studying neural encoding of signals in quiet and noise within the central auditory system. CAEPs tend to exhibit greater amplitudes compared to cochlear and auditory nerve evoked potentials, making them an attractive means to study the MOCR. Additionally, certain CAEPs including the P1, N1, and P2 components are sensitive to SNRs (Billings et al., 2009; 2013; Papesh et al., 2015; Small et al., 2018). Given that the MOCR is thought to modify SNR, CAEPs may offer a powerful approach to assessing the human MOCR in relation to unmasking.

Non-MOCR CAEP studies report changes in P1, N1, and P2 amplitudes and latencies in response to changes in SNR. The presence of noise degrades the response, resulting in reduced amplitudes and prolonged latencies compared to quiet environments (Billings et al., 2009; Whiting et al., 1998; Kaplan-Neeman et al., 2006). Consistent with

this, as SNR decreases, CAEP amplitudes decrease and latencies increase (Billings et al., 2009; Papesh et al., 2015; Small et al., 2018).

Despite their sensitivity to SNRs, few studies have examined the effect of MOCR on CAEP amplitude and latencies. Desmedt (1962) conducted a study investigating the modulation of the efferent system across the auditory pathway, from the cochlea to the auditory cortex, utilizing auditory evoked potentials amplitude. The study examined the response to a click stimulus when OCB stimulation was applied throughout the entire auditory pathway, including the round window, superior olive, inferior colliculus, and auditory cortex. The findings revealed that the introduction of OCB stimulation resulted in a reduced response, indicating the impact of the efferent system. Rao and colleagues (2020) conducted a study to examine the effect of the efferent system on central auditory processing. They measured the amplitude and latency of P300 responses when contralateral acoustic stimulation was presented. Results showed that when contralateral acoustic stimulation was presented simultaneously to both ears, there was a reduction in amplitude and an increase in latency of approximately 35 ms specifically in the left ear. These findings provide compelling evidence of the efferent system's influence on the auditory cortex.

Role of the MOCR in Humans

Informed from animal work, the function of MOCR in humans is divided into two roles: protecting the ear from acoustic trauma and aiding signal detection (including speech perception) in noise. Each of these purported roles are discussed below. However, specific focus is directed on the possible role of the MOCR in aiding signal detection in noise, as this is the area addressed by the dissertation research.

Protection of the Ear from Noise

Animal studies suggest that the MOCR increases resistance to NIHL (Cody & Johnstone, 1982; Reiter & Liberman, 1995; Attanasio et al., 1999; Maison & Liberman, 2000; Luebke & Foster, 2002; Luebke et al., 2014; Liberman et al., 2014; Boero et al., 2018). Conversely, human studies encounter limitations when attempting to establish conclusive evidence for any MOCR-mediated protective effects on human ears due to the inability to utilize noise levels that induce hearing loss. Nevertheless, drawing from various animal studies, it has been observed that a stronger MOCR feedback corresponds to enhanced defense against acoustic trauma. To apply this knowledge to humans, one method is to employ OAE, a conventional approach for assessing MOCR in human subjects. Activation of MOCR diminishes the magnitude of OAE, further supporting the notion that it reduces cochlear amplification (Guinan, 2006). Generally, greater MOCR strengths yield more substantial changes of magnitude and phase in OAE (Guinan et al., 2003; Backus & Guinan, 2006; Mertes, 2018). Another study by Veuillet et al., (2001) examined the association between OAE and MOC responses following noise exposure in both a normal ear and a group with unilateral hearing loss (i.e., affected ear). Click-

evoked otoacoustic emissions (CEOAE) were assessed, and thresholds at 4, 6, and 8 kHz were found to increase after noise exposure, with the most significant threshold shifts observed at 6 kHz. Specifically, immediately after noise exposure, the affected group exhibited a smaller amplitude compared to the normal group. However, hearing recovered based on measurements taken 30 days later. Sliwinska-Kowalska & Kotylo (2002) examined the correlation between the efferent system and OAE in workers. The study revealed that individuals exposed to noise exhibited reduced efferent suppression of DPOAE, with the suppression being more pronounced when the louder levels of 40- and 70-dB SPL were employed in the current investigation. Thus, based on these studies including humans and animals, MOCR in humans may protect the ears from acoustic injuries.

Detection Signal in Noise

Another hypothesized role of the MOCR in humans is to aid signal detection, including speech perception, in noise. Two approaches have been used to investigate how the function of MOCR affects human behavioral responses: using tones (e.g., simple signals) and speech. Micheyl et al. (1995) and Micheyl and Collet (1996) showed a relationship between tone-detection thresholds and MOCR-OAE suppression in background noise, indicating that detection thresholds improved with increased OAE suppression. The higher the MOCR effect, the greater the OAE attenuation, and the more sensitive threshold and better performance of tone detection due to MOCR activation. Marrufo-Pérez and colleagues (2021) conducted a study examining the relationship between MOCR induced changes in behavioral response and the OAEs. They observed that activation of the MOCR using contralateral noise led to an increase in tone detection thresholds, indicating reduced sensitivity, and a decrease in OAE levels. These findings indicate that the activation of the efferent system through MOCR brings about changes at both the pre-neural and neural levels. Nevertheless, the study did not find a significant correlation between MOCR changes in thresholds and OAEs.

The role of the MOCR in speech perception has been studied using various speech sounds including syllables, words, and sentences. Giraud et al. (1997) studied the correlation between the MOCR effect and speech perception in noisy environments. They measured speech-in-noise intelligibility (syllabic) for two groups: individuals with normal hearing and individuals with a cut efferent pathway stemming from unilateral section of the VIIIth nerve. The results showed that word recognition in noise scores increased significantly, by between 15% and 24%, with an intact MOCR. In the same study, no significant elevation was observed in patients with a sectioned vestibular nerve (intact cochlear nerve), suggesting that an intact olivocochlear efferent system enhances speech perception abilities in a noisy environment.

de Boer et al. (2008) showed a positive correlation between speech-in-noise performance (consonant-vowel tokens [bi:]/[di:]) and the amount of MOCR-induced OAE suppression. However, de Boer et al. (2012) showed a negative correlation between speech-in-noise performance (consonant vowel tokens [da:]/[ga:]) in noise and the

amount of MOCR-induced OAE suppression due to MOCR activity. These two studies demonstrated different outcomes even though they used similar types of equipment, procedures, and phoneme discrimination behavioral tasks. The only difference between the two studies were the syllables for measuring speech-in-noise performance. According to these findings, MOC activation does not always improve speech in noise performance. Taken together, the cause of discrepancies in the study results remained unclear. Recent studies by Mertes and Stutz (2023) suggest that there is no substantial correlation between MOCR strength and sentence recognition in noise. Hence, in such cases, the MOCR might not consistently enhance speech perception capabilities in noisy environments. This observation suggests the presence of additional factors that could influence outcomes, potentially unrelated to the benefits associated with MOCR activation.

Kumar and Vanaja (2004) investigated the effect of contralateral acoustic stimulation on speech performance. The study used different conditions: quiet and noisy environments with and without MOCR activation. The results show that MOCR activation led to improved speech perception in noisy environments at SNRs of 10 dB and 15 dB. These findings imply that MOCR plays an unmasking function in speech perception in noisy situations. A study by Mertes et al. (2019) also examined the impact of the olivocochlear efferent system on speech recognition in noisy environments. The researchers assessed speech perception abilities under varying SNRs (ranging from 12 to 0 dB) in the ipsilateral ear, both with and without MOCR activation by contralateral noise. The findings demonstrated a significant improvement in speech performance when the MOCR was activated, particularly at the lowest SNR.

In a study aimed at exploring the relationship between acceptable noise level (ANL) and MOCR in relation to noise tolerances, researchers investigated how individuals perceive and tolerate noise while listening to speech (Jamos et al., 2021). By examining the impact of MOCR activation on the output of the cochlea, it became possible to make predictions regarding individuals' levels of noise tolerance. Specifically, this study focused on the relationship between cochlear microphonic (CM) amplitude and ANL during MOCR activation. The results indicated a significant increase in CM amplitude, particularly among individuals with low ANL scores compared to moderate ANL, suggesting a higher tolerance for louder noise. These findings provide evidence that when the MOCR is activated, humans exhibit reduced cochlear amplification, enabling them to tolerate louder levels of noise.

Based on the findings presented above, there is evidence to support MOCR-mediated unmasking in humans. However, results have not been consistent across studies. This suggests the presence of factors unrelated to the MOCR efferent effect, perhaps related to cognition, test difficulty, among others. Majority of studies have relied on OAEs as an objective evaluation of the MOCR; however, as discussed, OAEs provide only a pre-neural assay. Unmasking occurs at the neural level and neural based assays may therefore be more beneficial in studying the human MOCR.

Perhaps attention plays a role in these inconsistent results. Measuring the effectiveness of MOCR using OAEs does not require active concentration. However, with behavioral tests, results can be influenced by the level of attention that individuals exhibit during the testing process. The efferent system can be more active during selective attention compared to non-attention (Walsh et al., 2014). When selective attention was requested in a study that required recognition of the middle 5 digits of a 7-digit string, the response of SFOAE differed by 1.3-4 dB, which shows more reduction compared to non-attention. MOC neurons are influenced by the descending auditory system, and there is also evidence that these descending activities may be involved in attentional control (reviewed by Meric & Collet, 1994).

CHAPTER 3. RATIONALE AND OVERVIEW OF DISSERTATION RESEARCH

Overview of Study

As previously discussed, the role of the human MOCR remains unclear, possibly due to an over-reliance on OAEs for investigation. OAEs provide only a pre-neural assay of the MOCR. However, unmasking is presumed to occur at the neural level. Neural assays of the MOCR have primarily relied on the cochlear microphonic and compound action potential. However, these potentials are not robust in humans. CAEPs may provide an alternative means to assay the human MOCR as it relates to unmasking. CAEPs are non-invasive tools and can provide insight into the cortical response to signals in noise. Additionally, CAEPs are larger amplitude responses compared to cochlear and auditory nerve auditory evoked potentials.

Two classes of CAEPs include the middle and late latency response (LLR). Latency refers to onset of the response relative to sound onset. In the current study, the LLR was measured and used to assay the MOCR. The LLR includes three components: P1, N1, and P2. The first positive peak voltage component is known as P1, has a latency near 50 ms, and originates from the primary auditory cortex (Howard et al., 2000). The second, a negative peak voltage component, referred to as N1 (Davis, 1939), is measured at 100 ms. N1 originates from auditory cortex including frontocentral and midtemporal area (Pratt & Lightfoot, 2012). The third component, P2, is a positive peak voltage component that occurs around 200 ms and represents the multiple area response including both primary and secondary auditory cortex.

Especially relevant to the role of the MOCR in speech perception in noise, the LLR is sensitive to SNRs. Billings et al. (2009; 2013) have provided evidence for the sensitivity of LLR to SNR, in that the LLR shows an increase in amplitude and a decrease in latency as SNR improves. These changes are consistent with stronger neural encoding of the signal as SNR improves. Additionally, Papesh et al. (2015) have demonstrated higher amplitudes and shorter latencies with higher SNRs. Small et al. (2018) used speech stimuli at various SNRs to evoke the CAEP and also found higher amplitudes and shorter latencies as SNR increased. The sensitivity of CAEPs to SNR suggests that CAEPs may provide a way to evaluate the theory of MOCR-mediated unmasking in humans. The studies cited above manipulated SNR at the level of the ear canal through purposeful stimulus design. Assuming the MOCR manipulates SNR at the level of the VIIIth nerve, CAEPs should exhibit predictable changes in both amplitude and latency upon MOCR activation, namely, larger amplitudes and shorter latencies.

Figure 3-1 illustrates the hypothesized relationships between SNR, MOCR unmasking, and CAEPs. The white-filled arrow with a black line (1) represents the theoretical link between SNR and MOCR-mediated unmasking (Winslow & Sachs, 1987; Winslow & Sachs, 1988; Kawase et al., 1993). The black solid arrow labeled (2) highlights the known relationship between CAEPs and SNR (Billings et al., 2009; 2013).

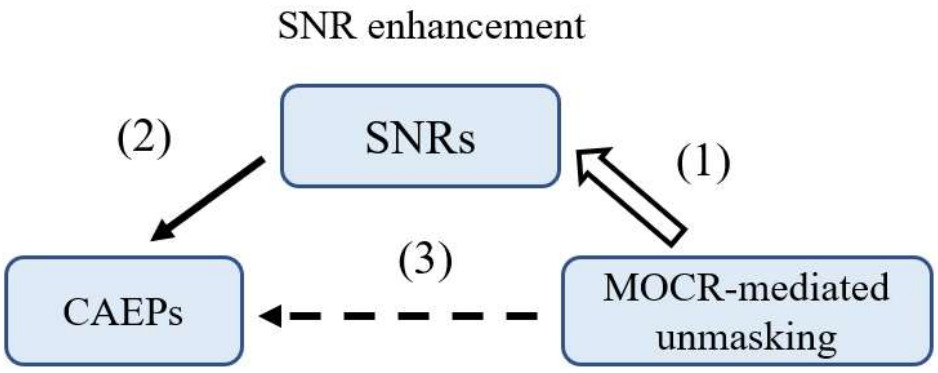

Figure 3-1. Hypothesized relationships between the MOCR, SNRs, and CAEPs. Each arrow represents a relationship: white-filled arrow with a broken black line (1) between MOCR-mediated unmasking and SNRs and black solid line (2) between SNRs and CAEPs. The black dashed (3) arrow represents our hypothesis that MOCR-mediated unmasking directly affects CAEPs.

If MOCR unmasking does occur in humans, we can expect CAEPs evoked by a signal in noise to exhibit larger amplitudes and shorter latencies upon MOCR activation due to an MOCR-mediated enhancement in SNR. This final hypothesized relationship is illustrated by the black dashed line (3).

The studies noted above demonstrate that higher SNRs result in increased amplitude and shorter latency CAEPs. However, these studies, which directly manipulated SNR, do not address the potential role of the MOCR in altering SNRs. As such, they do not provide insight into MOCR function in humans. Therefore, the objective of this study was to examine whether MOCR-mediated unmasking is evident in human CAEPs for signals in quiet and in noise. In addition to CAEPs, the current study employs OAEs, a pre-neural response, and tone-detection, a behavioral response, to gain deeper insights into possible MOCR-mediated unmasking and relationships between various approaches to assay the human MOCR. This research will contribute to a better understanding of how the MOCR influences the ability to perceive masked signals.

Research Questions

There are two aims of this study: (1) evaluate the effect of MOCR activation on CAEPs to tones in a quiet environment and (2) evaluate the effect of MOCR activation on CAEPs to tones in a noisy environment. Research questions for each aim are as follows:

- Aim 1: Do CAEPs provide evidence of SNR reduction for a tone in quiet during MOCR activation?
- Aim 2: Aim 2: Do CAEPs show evidence of SNR improvement for a tone in noise during MOCR activation?

Hypotheses

The hypothesis of the first aim is that CAEP amplitude decreases and latency increases during MOCR activation for a tone in quiet because the MOCR reduces the cochlear response to the tone, consistent with SNR reduction. The hypothesis of the second aim is that CAEP amplitude increases and latency decreases during MOCR activation for a tone in noise because the efferent system provides unmasking at the neural level, which improves SNR.

CHAPTER 4. EXPLORING SIGNAL-TO-NOISE RATIOS (SNRS) REDUCTION THROUGH CAEP: INSIGHT FROM THE AUDITORY EFFERENT SYSTEM IN A QUIET ENVIRONMENT

Introduction

In the first experiment, a tone burst in quiet was presented to the subject's ipsilateral ear; noise was presented to the contralateral ear to activate the MOCR. The research question was: Do CAEPs provide evidence of SNR reduction for a tone in quiet during MOCR activation? The hypothesis was that CAEP amplitude decreases and latency increases during MOCR activation.

Figure 4-1 shows the predicted effect of MOCR activation on the rate-level function of a Type I afferent auditory neuron, responding to a tone presented in a quiet environment. This rate-level function was modeled based on direct measurements of auditory neuron firing with and without electrical stimulation of the MOC efferent system in animals (Winslow & Sachs, 1988). In detail, for a tone in quiet and in the absence of MOCR activation, the neuron's firing rate increases once the tone's level exceeds the neuron's threshold. The firing rate continues to increase as the tone's level increases until the tone's level reaches the neuron's saturation level. As the tone's level increases beyond the neuron's saturation level, the firing rate of the neuron remains nearly constant. When the MOCR is activated, the rate-level function shifts horizontally (as shown by the red solid line) because the MOCR reduces cochlear amplification, thereby decreasing cochlear output and, by extension, input to the neuron. As a result, both the threshold and saturation level of the neuron increase. In the example shown in the left panel, the neuron's threshold is 15 dB SPL and saturation occurs at 70 dB SPL in the absence of MOCR activation (see blue solid line in the left panel). If the MOCR reduces cochlear output by 15 dB (hypothetically), the neuron's threshold and saturation level are expected to increase by 15 dB. Therefore, the new threshold of the neuron upon MOCR activation is 30 dB SPL, and the saturation level is 85 dB SPL. Due to the MOCR-induced change in the neuron's threshold, sound levels exceeding the threshold will result in a reduced firing rate, when compared to those same sound levels in the absence of MOCR activation.

To compare the extent to which the SNR changes upon MOCR activation, the discharge rate of the neuron in response to the tone can be compared to the neuron's spontaneous rate, with and without MOCR activation. The middle panel shows a comparison of SNR at the neural level across input sound levels between MOCR active and inactive conditions. Two lines demonstrate similar trends in which the improvement of SNR at neural levels increases as the input signal level increases. However, the red dashed line, featuring the MOC system, exhibits a rightward shift of 15 dB because of reduced cochlear amplification and input to the neuron. The right panel shows the difference in neural SNR between no MOCR activation and MOCR activation. Across the neuron's dynamic range, MOCR activation causes a reduction in SNR. For this

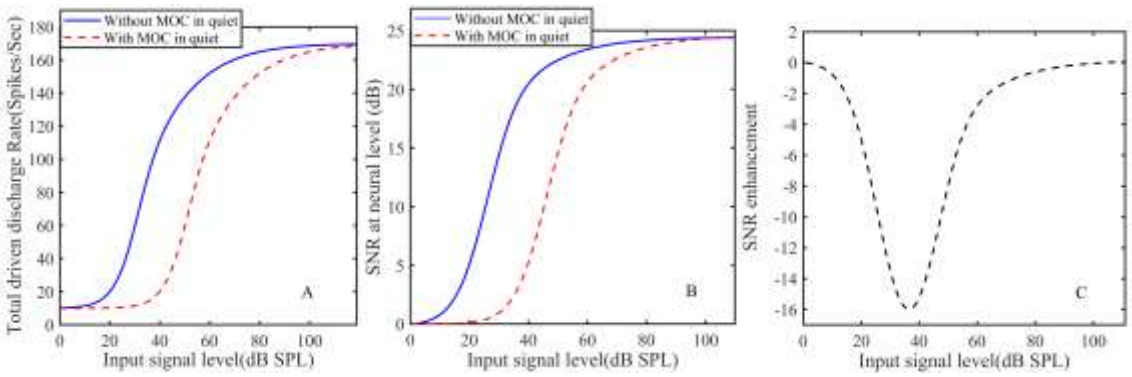

Figure 4-1. Schematic of the mid-spontaneous fiber rate-level function in quiet with and without MOCR.

The blue solid line shows the neuron's rate-level function response to a tone in quiet, without MOCR activation. The red dashed line shows the neuron's rate-level function response to a tone in quiet during MOCR activation. In the middle panel, the blue solid line shows SNRs at the neural level without MOCR activation, while the red dashed line shows SNRs at the neural level with MOCR activation. In the right panel, the black dashed line indicates the difference in neural SNRs between no-MOCR activation and MOCR activation. Negative values indicate a decrease in SNR upon MOCR activation.

example, the highest SNR reduction occurs at a 40 dB input signal level: At this input level, the neural SNR during MOCR activation is 16 dB lower than that without MOCR activation. These simulations suggest that activation of the MOCR in a quiet environment result in reduced neural SNRs.

If the MOCR alters the SNR at the auditory nerve level (as illustrated in the left panel), the LLR, which includes the components P1, N1, and P2, are hypothesized to exhibit predictable changes in amplitude and latency. Billings et al. (2009; 2013) have demonstrated that certain CAEPs are sensitive to SNR, in that latencies decrease and amplitudes increase as SNR increases. From the theoretical model presented in **Figure 4-1**, we can predict how the LLR is changed upon MOCR activation. Specifically, upon MOCR activation for a tone in quiet, LLR amplitudes are hypothesized to decrease, and latencies increase because of a reduced SNR.

Methods

Research Design

The primary objective of this study was to test the overall hypothesis that the MOCR provides unmasking. This primary means by which this hypothesis is tested is through the LLR, which is sensitive to SNR (Billings et al., 2009), providing a neural assay of possible unmasking (**Figure 4-2**). We employed an LLR technique to measure the latency of P1, N1, and P2, as well as the inter-amplitude of P1-N1 and N1-P2. Supplementary assays of the MOCR were also performed, including a pre-neural assay and a behavioral assay. The pre-neural assay aimed to measure the effects of the MOCR on cochlear response prior to the neural level. Pre-neural responses were evaluated using OAE, a widely employed method in pre-neural assessments. The behavioral assay included a tone-detection in noise test with and without MOCR activation. The purpose of including the pre-neural and behavioral assays was to evaluate the potential relationship between various approaches to assaying the MOCR and determine if they provide similar insight.

Through the tests highlighted in **Figure 4-2**, we can enhance our understanding of how MOCR-mediated unmasking is evidenced in different areas of the auditory system, including human behavior. Additionally, both the pre-neural and behavioral assays are widely used as a tool to evaluate the MOCR and provide a means to demonstrate MOCR activity, where the neural response is more experimental.

Subjects

In this study, 50 individuals with normal hearing (age range = 18 – 44 years, mean age = 24.9) were recruited (**Table 4-1**). However, three subjects were excluded from the

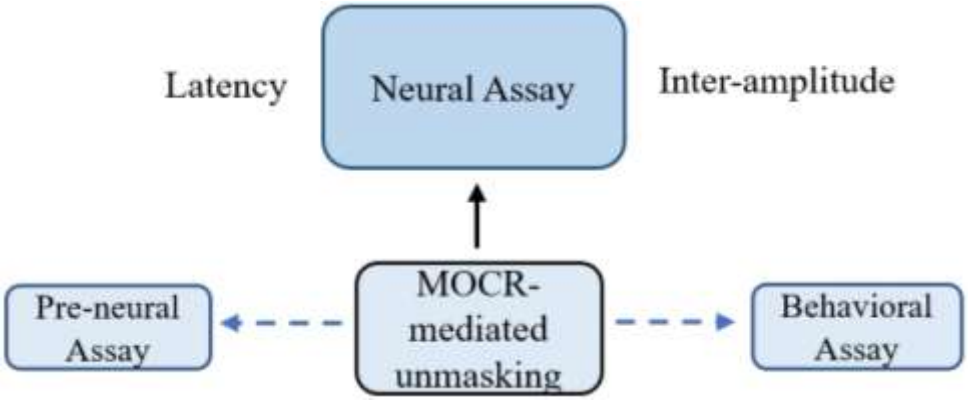

Figure 4-2. Diagram illustrating various assays of the MOCR.
The neural assay included measurement of LLR latencies and inter-amplitudes with and without MOCR activation. The pre-neural assay included an OAE-based test of the MOCR. The behavioral assay included a tone-detection task with and without MOCR activation. The primary focus was the use of the neural assay to evaluate the theory of MOCR-mediated unmasking.

Table 4-1. Distribution of subjects.

Age range	Subjects (n)	Females (n)	Right test ear (n)
19 - 23	20	20	11
24 – 28	19	15	6
29 – 33	7	6	3
34 - 38	1	1	1

Note: Three out of the initial 50 subjects were excluded from the analysis due to calibration errors.

analysis: one subject did not complete the test, and calibration errors in the behavioral test were identified for another two subjects. The target number of participants was 44 as determined from a power analysis based on the predicted MOCR-induced SNR change and the corresponding effect on N1 latency. Previous research by Micheyl and Collet (1996) reported a 1.79 dB improvement in behavioral tone-in-noise thresholds upon MOCR activation, suggesting close to a 2-dB SNR change due to MOCR activation. Knowing the predicted MOCR-induced change in SNR, we can estimate the predicted change in CAEP latency to inform a power analysis.

Billings and colleagues (2009) investigated how SNR affects the latency and amplitude of CAEPs and observed that as SNR increased from -5 to +20, N1 latency decreased by approximately 24 ms. Assuming that MOCR activation alters SNR by at least 2 dB, the predicted effect size on N1 latency from Billings et al. (2009) is 4.9 ms (i.e., N1 latency changes by 4.9 ms for every 2-dB change in SNR). Using an effect size of 4.9 ms, mean N1 latency of 126.5 ms (based on data from Billings et al. for an SNR of -5 dB), and standard deviation of 11.5 ms, 44 subjects are required to achieve a statistical power of 80% and an alpha level of 0.05. The reason for choosing N1 latency for the power analysis is that N1 showed a larger and more consistent waveform compared to other LLR components (P1 and P2). Additionally, N1 is highly correlated with behavioral testing (e.g., speech perception in noise; Parbery-Clark et al., 2011; Billings et al., 2013), which the MOCR is thought to improve.

Normal hearing was defined based on the outcomes of three screening tests: otoscopy, pure-tone audiometry, and tympanometry. All ear canals were required to be clear of occluding cerumen. Pure-tone audiometric thresholds were required to be no worse than 20 dB HL from 0.25 Hz to 8 kHz (1-octave steps), including 3- and 6-kHz, bilaterally. 226-Hz tympanograms were required to be type A (peak pressure: ± 100 daPa, ear canal volume: 0.9–2ml, and static admittance: 0.2–1.7 mmho). Informed consent was obtained prior to screening. Subjects who met the inclusion criteria participated in the data collection procedures, which included otoacoustic emission testing (pre-neural assay of the MOCR), tone-detection in noise (behavioral assay of the MOCR), and electrophysiologic testing (neural assay of the MOCR).

All testing was performed in a double-walled, electrically shielded, sound-treated booth. Subjects were seated in a chair during the testing and were instructed to remain quiet, awake, and still. During electrophysiologic testing, subjects watched a muted, closed-captioned movie of their choice to reduce the risk of falling asleep. Chambers et al. (2012) found that awake mice exhibit stronger efferent suppression of DPOAEs compared to anesthetized guinea pigs. Additionally, Aedo et al. (2015) showed that awake chinchillas display greater efferent suppression of the CAPs response than anesthetized chinchillas. Studies have shown that the effect of the MOCR may also be reduced by sleep in humans (Froehlich et al., 1993). Therefore, it was expected that efferent effects would be greatest if subjects remained awake during testing. One study involving P300 during CAEP demonstrated larger waveforms during wakefulness (Hull & Harsh, 2001). Data collection required approximately 3.5 hours over the course of a

single visit. The institutional review board (IRB) at the University of Tennessee Health Science Center approved the research protocol (IRB number: 22-09163-XP).

Cortical Auditory Evoked Potentials (CAEPs)

Equipment

The LLR was measured for the subjects' ipsilateral ear using a 2-channel s (Navigator PRO system [Bio-logic]) (**Figure 4-3**). The ipsilateral ear is chosen at random, while the opposite ear is referred to as the contralateral ear. The first channel recorded electrical activity from an electrode montage with the non-inverting electrode on the vertex (Cz) and the inverting electrode on the nose. The second channel recorded electrical activity from an electrode montage with the non-inverting electrode on the high-forehead (Fz) and the inverting electrode on the nose. The ground electrode was on the low forehead (Fpz). The impedance of all electrodes was ≤ 5.0 kΩ, and the difference between each electrode's impedance was within the range of $1 – 2$ kΩ. All recordings were amplified and converted from analog to digital. Common-mode rejection was used to reduce noise. The signal was amplified with 50,000x gain. The artifact rejection level was initially set to 72 μV, however, the level was adjusted for each individual to ensure that recordings with eye-blinks were rejected. The LLR was filtered using a band-pass filter with a passband from 1 to 30 Hz. Soft foam tips coupled to insert earphones were placed in both ear canals.

Measurement conditions

The LLR was measured from the ipsilateral ear in response to 70-ms, 1-kHz alternating-polarity tone bursts (50-ms plateau and 10-ms rise/fall). Tone bursts were presented to the ipsilateral ear at a rate of 1.1/s and a level of 60 dB SPL. The purpose of choosing 1-kHz tone bursts to elicit the LLR was based on findings suggesting this region of the cochlea has a high MOC neuron innervation density (Liberman & Liberman, 2019). As MOC innervation density increases, MOC-evoked suppression also increases, resulting in larger changes to the auditory-evoked response (Liberman et al., 2014). To examine the effect of MOCR activation on the LLR, we measured the LLR with and without 60 dB SPL contralateral noise. In the absence of contralateral noise, the MOCR is expected to be inactive. In contrast, when the contralateral noise is present, the MOCR is expected to be active. The level of the noise (60 dB SPL) was chosen as it should activate the MOCR without concurrent activation of the MEMR (Davies, 2016). The noise was white noise. The level of the tone bursts and noise were measured using an IEC 60318-4 Ear simulator RA0045, accompanied by a sound level meter (Larson Davis system 824). The order of the MOCR conditions (i.e., active and inactive) was randomized for each subject. To increase reliability and improve waveform morphology, LLR was measured for each MOCR condition at least 4 times using 200 sweeps per replication. In some cases, if the replications were inconsistent, a 5^{th} replication was made and only the best 3 or 4 were included and averaged all replication together in the final analysis.

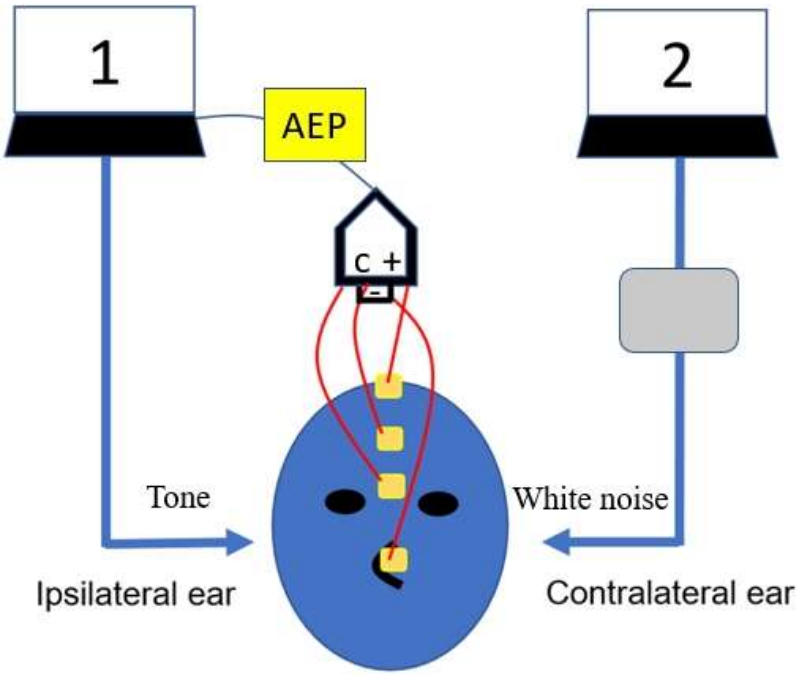

Figure 4-3. Experimental setup for CAEP in Aim 1.
The system involved the following steps: (1) the computer sent a 1-kHz tone to the ipsilateral ear via an insert earphone (Bio-logic) and recorded LLR, and (2) the computer provided white noise to the contralateral ear via ER3C insert earphone (Etymotic research). The gray box represents the function generator (Tektronix-AFG2021C), which was controlled by (2) the computer. It was utilized to generate noise and deliver it to the contralateral ear. The yellow box represents the AEP system used for recording LLR: c =ground, +=non-inverting electrodes, and -=inverting electrodes. Four electrodes were attached to the participant's head: one on the vertex as a positive input on channel 1, one on the high forehead as a positive input on channel 2, one on the low forehead as ground, and one on the nose as a negative input on channels 1 and 2 using a jumper.

Analysis

LLR was recorded spanning a time window from 30 to 300 ms. The amplitudes and latencies for P1, N1, and P2 were analyzed for all measurement conditions. Two examiners analyzed LLR recordings and agreed upon final identification of the P1, N1, and P2 components, when present. The P1-N1 and N1-P2 inter-amplitudes were calculated as the difference between peak-to-trough and trough-to-peak, respectively (**Figure 4-4**). **Figure 4-4** provides an explanation of how the latency and inter-amplitude of the LLR were computed. Latency is determined by measuring the time interval between the stimulus onset and each peak. Additionally, the inter-amplitude is calculated by measuring the distance between the P1 and N1 peaks, as well as the distance between the N1 and P2 peaks.

Otoacoustic Emissions (OAEs)

A pre-neural, TBOAE was performed on all subjects. The purpose was to allow for correlation analysis between the OAE-derived MOCR effects and those for the neural and behavioral assays.

Equipment

Stimulus presentation and data acquisition were controlled through a lab computer (Windows 10 operating system) running the ARLas software (Goodman). The equipment used included: (1) a 24-bit sound card (RME Babyface, 48-kHz sampling rate) connected to the computer via USB: The sound card converted the stimulus from a digital to an analog signal, and ear canal sound pressure from an analog to a digital signal. (2) An ER-10B+ probe microphone assembly (Etymōtic Research, Inc.): The probe measured and amplified (+20-dB gain) ear-canal sound pressure recordings in the ipsilateral ear. (3) A pair of ER-2 insert earphones (Etymōtic Research, Inc): The insert earphones were coupled to the ear canal using ER10-14 foam ear tips and delivered stimuli to the subject's ears (ipsilateral ear for tone-bursts and contralateral ear for noise). The noise presented in the contralateral ear was generated using an arbitrary function generator (Tektronix-AFG2021C), which was controlled by MATLAB, and transmitted via the second ER-2 transducer.

Measurement conditions

1-kHz, 5-cycle, 75-dB SPL tone-bursts were presented to the subject's ipsilateral ear at a rate of 13/s. The ipsilateral ear was chosen randomly for each subject and corresponded to the ipsilateral ear used for LLR measurement. TBOAEs were measured with and without broadband noise presented to the contralateral ear. The noise was generated similarly to that used for LLR measurement. The noise was turned on (activating the MOCR) and off (deactivating the MOCR) every 10 seconds. This pattern was repeated 12 times. A minimum of 4,096 recordings were made for each MOCR condition (2,048 with and 2,048 without contralateral noise). The duration of testing was

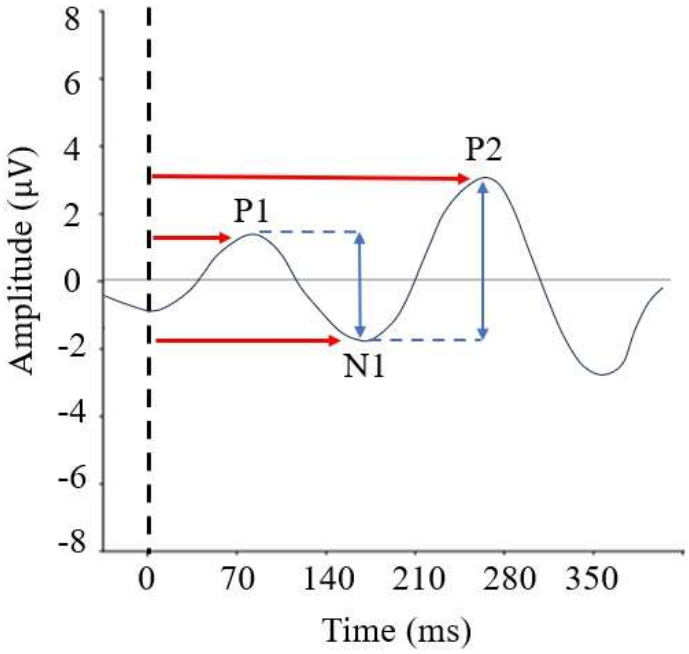

Figure 4-4. Calculation of latency and inter-amplitude.
This Figure illustrates the approach to calculating LLR component amplitudes and latencies. The black dashed line indicates the stimulus onset, while the red solid line indicates the time difference from the stimulus onset to each peak, corresponding to component latency. Additionally, the blue solid line represents the inter-amplitude, which is the amplitude difference between adjacent components.

approximately 5 minutes. Stimulus onset jitter was applied to reduce contamination from synchronized spontaneous otoacoustic emissions (Lewis, 2020).

Analysis

The TBOAE was analyzed from the raw data using custom-written MATLAB code. Since the raw data includes non-TBOAE components such as tone burst sound pressure and residual stimulus artifacts, the ear canal sound pressure recordings were truncated to remove the initial 9-ms prior to further analysis. The initial and final 1.5 milliseconds of the analysis window were ramped on and off using a ½-cycle Hann window. A bandpass filter was applied to isolate OAE energy around 1-kHz (256 order for 1-kHz center frequency and 2 octave bandwidth). Artifact rejection was performed to eliminate recordings with root mean square (RMS) levels exceeding the 1.5x interquartile range. Subsequently, sound pressure recordings were divided into two buffers including the odd-numbered and even-numbered recordings. The signal (OAE) was calculated as the average across the buffers and the noise is calculated as the difference in the average waveforms between buffers, divided by $\sqrt{2}$. The SNR was calculated as the dB difference between the signal RMS level and noise RMS level. MOCR strength was calculated as the dB-change in OAE level between MOCR conditions. In **Equation 1-1**, $tboae_{without\ MOCR}$ indicates sound-pressure time waveforms without MOCR activation and $tboae_{with\ MOCR}$ indicate sound-pressure time waveforms with MOCR activation. MOCR strength ($\bar{\Delta}_M$) was expressed in dB and calculate as:

$$\bar{\Delta}_M = 20 \times \log_{10}\left(\sqrt{\frac{\sum(tboae_{without\ MOCR})^2}{\sum tboae_{with\ MOCR}{}^2}}\right) \qquad \textbf{(Eq. 1-1)}$$

MOCR strength was analyzed only when the TBOAE SNR (measured in the absence of contralateral noise) was at least 15 dB. High SNRs are necessary to have confidence that small changes in the OAE in MOCR assays are merely due to noise in individuals (Goodman et al., 2013).

Inadvertent activation of the MEMR by the contralateral noise was taken into consideration when analyzing the data because the MEMR can reduce TBOAE amplitude and lead to erroneous interpretations. To avoid activation of the MEMR, the noise did not exceed 60 dB SPL, which is typically below the threshold of the human MEMR thresholds (Margolis & Fox, 1977). Consequently, the noise level employed in the current study is not expected to potentially trigger MEMR.

Tone-detection

In addition to the LLR and OAE testing, all subjects also performed a tone detection task with and without activation of the MOCR. The purpose was to allow for correlation analysis between the tone-detection-derived MOCR effect and the other MOCR metrics (LLR and OAE). The behavioral testing allowed for the examination of both peripheral and central auditory processing in response to the MOCR-mediated

unmasking effects. As a result, it was possible to investigate how MOCR-mediated unmasking affects individual behavioral outcomes in practice.

Equipment

The test was conducted using MATLAB software to control stimulus presentation and data acquisition on a lab computer running Windows 10 operating system. The equipment includes: 1) a 24-bit sound card (RME Babyface, with a 48-kHz sampling rate) connected to the computer via USB, 2) insert earphones (ER-2) placed in the ear canals to deliver stimuli to the subject's ears (ipsilateral ear for 1-kHz tone-burst and contralateral ear for noise), 3) a monitor used to present the testing interface to the subject, and 4) an arbitrary function generator (Tektronix-AFG2021C) to generate noise for activation of the MOCR.

Measurement conditions

The participant listened for a tone in the ipsilateral ear with and without contralateral noise. The tone was a 1 kHz tone burst with a duration of 70 ms, and the initial level was set at 48.3 dB SPL. The noise was generated similarly to that described previously. A 3 alternative-forced choice paradigm was used to determine thresholds. Subjects listened for a tone present in 1 of 3 listening intervals. Subjects were provided with the following instructions:

"You will hear a tone and noise, and then look at the monitor, which displays three boxes. The boxes will flash with or without sound. Once all three boxes have flashed, you will be asked to click the box that contained the tone using the mouse. The first two trials will be a practice session, followed by the actual test. Although you may hear noise occasionally, your task is to focus solely on identifying the tone"

A total of ten blocks were conducted, consisting of five blocks each for the MOC active and MOC inactive conditions. Five reversals were required for completion of a single block. When the subject provided the correct response, the tone level was reduced by 4 dB. In the case of an incorrect response, the tone level was increased by 2 dB. Blocks were randomized for each subject. Due to the subjective nature of the test, factors such as attention and environment could affect the results. Therefore, we periodically monitored the participant's condition, as the test could be lengthy and tiring.

Analysis

There was a total of 10 threshold measurements, called 10 blocks. Ten blocks were conducted, with 5 blocks for MOCR activation and 5 blocks for no-MOCR activation. The threshold for each of the 5 blocks were calculated. We observed that the standard deviation of the 5 thresholds exceeded 2 dB for certain participants. However, upon removing the first block, the average standard deviation (SD) of the remaining 4 blocks decreased by over 15% in comparison to the 35% average of all 5 blocks. Although it still exceeds a 2 dB SD in 15% of total trials, incorporating the average of other trials can

enhance confidence in the results. These findings suggest that the initial block's value influences the overall average, therefore, we calculate the average based on the remaining 4 blocks after removing the first block.

Statistical Analysis

The objective of this analysis was to investigate whether MOCR activation has a significant effect on LLR inter-amplitudes and latencies. A repeated measures analysis of variance (ANOVA) was employed with the MOCR condition (off and on) serving as the within-subject factor. The dependent variables consisted of LLR inter-amplitudes (P1-N1 and N1-P2) as well as latencies (P1, N1, and P2). Finally, linear regression analysis was also performed to examine the relationships among the various MOCR metrics, including neural, pre-neural, and behavioral assays.

Result

Aim 1 investigated the effect of MOCR activation on LLR latencies and amplitudes for a tone in quiet. The hypothesis was that the LLR component latencies will increase and inter-amplitude decrease upon MOCR activation due to reduced cochlear output, resulting in a reduced neural SNR.

A repeated measure ANOVA was performed to examine the effect of MOCR activation on LLR latency within subjects. For P1 latency, there was no statistically significant effect of MOCR ($F(1,46) = 0.175$, $p = 0.678$). Similarly, for N1 latency, no statistically significant effect of MOCR was observed ($F(1,46) = 1.500$, $p = 0.227$). Additionally, for P2 latency, there was no statistically significant effect of MOCR ($F(1,46) = 1.694$, $p = 0.200$).

Effect of MOCR on LLR Latency

Table 4-2 provides means and SDs for the average of the P1, N1, and P2 latency. **Figure 4-5** depicts the Box-and-whisker plot, illustrating the median P1, N1, and P2 latency for both MOCR off and on conditions. The plot includes the median, 1st- and 3rd-quartiles, 1.5×inter-quartile range, and outliers. The average P1 latency increased from 71.82 ms for the MOCR-off condition to 72.47 for the MOCR-on condition – an average increase of 0.64 ms. The average N1 latency decreased from 110.84 ms for the MOCR-off condition to 109.62 for the MOCR-on condition – an average decrease of 1.22 ms. The average of the P2 latency increased from 156.67 ms for the MOCR-off condition to 158.55 for the MOCR-on condition – an average increase 1.88 ms.

Table 4-2. Summary of the LLR latency in Aim 1.

	Components		
MOCR	**P1 latency (ms)**	**N1 latency (ms)**	**P2 latency (ms)**
Off	71.82 (15.57)	110.84 (9.2)	156.67 (13.79)
ON	72.47 (11.17)	109.62 (11.4)	158.55 (14.21)
Diff	0.64 (10.54)	-1.22 (6.82)	1.88 (9.91)
P	0.678	0.227	0.200

Note: Mean, SDs, difference, and *p*-value for P1, N1, and P2 both MOCR off and on. SDs are indicated in parentheses.

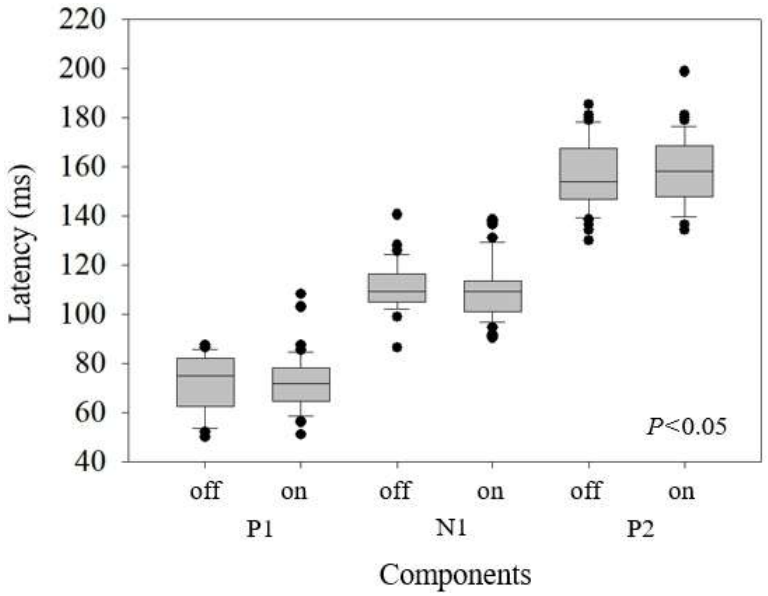

Figure 4-5. P1, N1, and P2 latency in Aim 1.
Box-and-whisker plot illustrating the median, interquartile range (shaded region), 1.5xinterquartile range (whiskers), and outliers (filled symbols) for P1, N1, and P2 latency for both MOCR off and on conditions.

Effect of MOCR on LLR Inter-amplitude

Table 4-3 provides means and SDs for the average of the P1-N1 and N1-P2 inter-amplitude (μV). **Figure 4-6** depicts the Box-and-whisker plots, illustrating the median P1-N1 and N1-P2 inter-amplitude (μV) for both MOCR off and on conditions. The plot includes the median, 1st- and 3rd-quartiles, 1.5×inter-quartile range, and outliers. The average P1-N1 inter-amplitude decreased from 1.13 (μV) for the MOCR-off condition to 1.05 (μV) for the MOCR-on condition – an average decrease of 0.09 ms. The average N1-P2 inter-amplitude (μV) decreased from 1.56 (μV) ms for the MOCR-off condition to 1.54 for the MOCR-on condition – an average decrease of 0.025.

A repeated measure ANOVA was performed to examine the effect of MOCR activation on LLR inter-amplitude. For P1-N1 inter-amplitude, there was no statistically significant effect of MOCR ($F(1,46) = 1.386$, $p = 0.245$). For N1-P2 inter-amplitude, there was no statistically significant effect of MOCR was observed ($F(1,46) = 0.064$, $p=0.801$).

Effect of MOCR on OAEs

Figure 4-7 depicts the Box-and-whisker plot, illustrating the distribution of OAE levels for both MOCR off and on conditions. The plot includes the median, 1st- and 3rd-quartiles, 1.5×inter-quartile range, and outliers. The average OAE level (dB SPL) decreased from 12.26 for the MOCR-off condition to 11.31 for the MOCR-on condition – an average decrease of 0.95 dB. All distribution were approximately normal based on the Shapiro-Wilk test ($p > 0.05$). Post-hoc paired-sampled *t*-tests were performed [OAE level for MOCR off vs on: $t(46) = 3.675$, $p<0.001$]. This demonstrates that the OAE is reduced upon MOCR activation.

Effect of MOCR on Tone-detection Thresholds

Figure 4-8 shows box-and-whisker plots displaying the distributions of tone-detection thresholds (dB) for MOCR off and on conditions. The average tone-detection threshold (dB) increased (worsened) from -65.11 for the MOCR-off condition to -64.11 for the MOCR-on condition – an average increase of 0.95 dB. All distribution were approximately normal based on the Shapiro-Wilk test ($p>0.05$). Post-hoc paired-sampled t-tests were performed to determine if the thresholds were different between MOCR condition and statistically significant differences were observed [tone-detection thresholds for MOCR off vs on: $t(46) = 3.675$, $p<0.001$]. These findings provide support for an increase in threshold, perhaps due to reduced SNR, when the MOCR is activated.

Table 4-3. Summary of LLR inter-amplitude in Aim 1.

	Components	
MOCR	**P1-N1 inter-amplitude (μV)**	**N1-P2 inter-amplitude (μV)**
Off	1.13 (0.53)	1.56 (0.92)
ON	1.05 (0.56)	1.54 (1.06)
Diff	-0.09 (0.5)	-0.025 (0.68)
P	0.245	0.801

Note: Mean and SDs for P1-N1 and N1-P2 inter-amplitude (μV). SDs are indicated in parentheses.

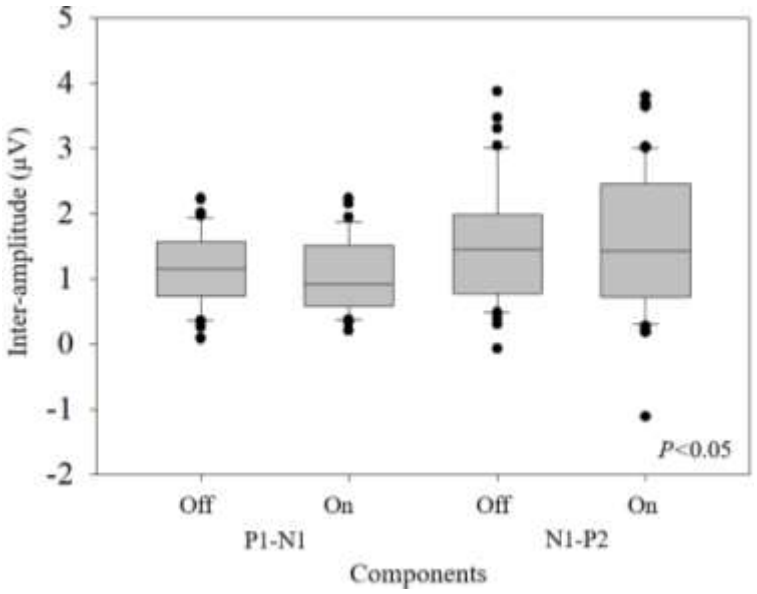

Figure 4-6. P1-N1 and N1-P2 inter-amplitude in Aim 1.
Box-and-whisker plot illustrating the median, interquartile range (shaded region), 1.5xinterquartile range (whiskers), and outliers (filled symbols) for P1-N1 and N1-P2 inter-amplitude (μV) for both MOCR off and on conditions.

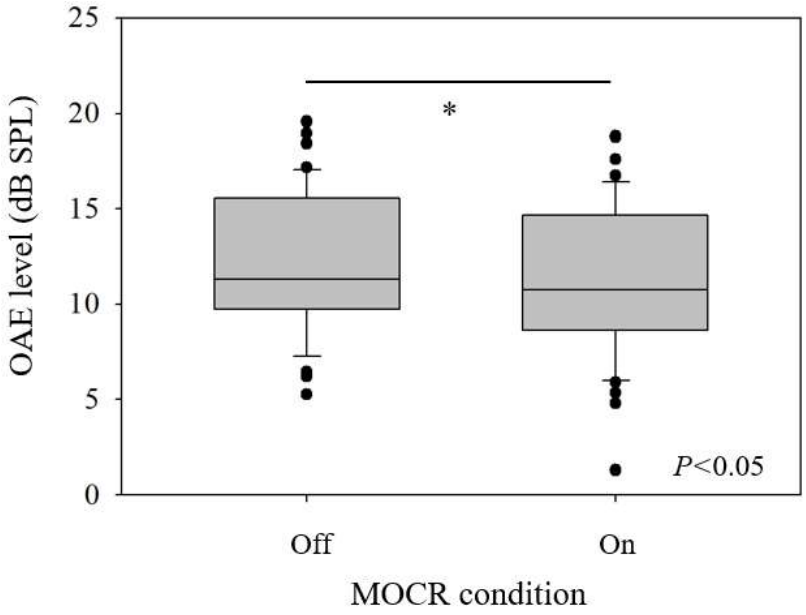

Figure 4-7. OAE level for both MOCR off and on.
Box-and-whisker plot illustrating the median, interquartile range (shaded region), 1.5 x interquartile range (whiskers), and outliers (filled symbols) for OAE level in dB SPL for both MOCR off and on conditions. Asterisks indicate a statistically significant difference at the $\alpha = 0.05$ level based on a paired-sampled *t*-tests.

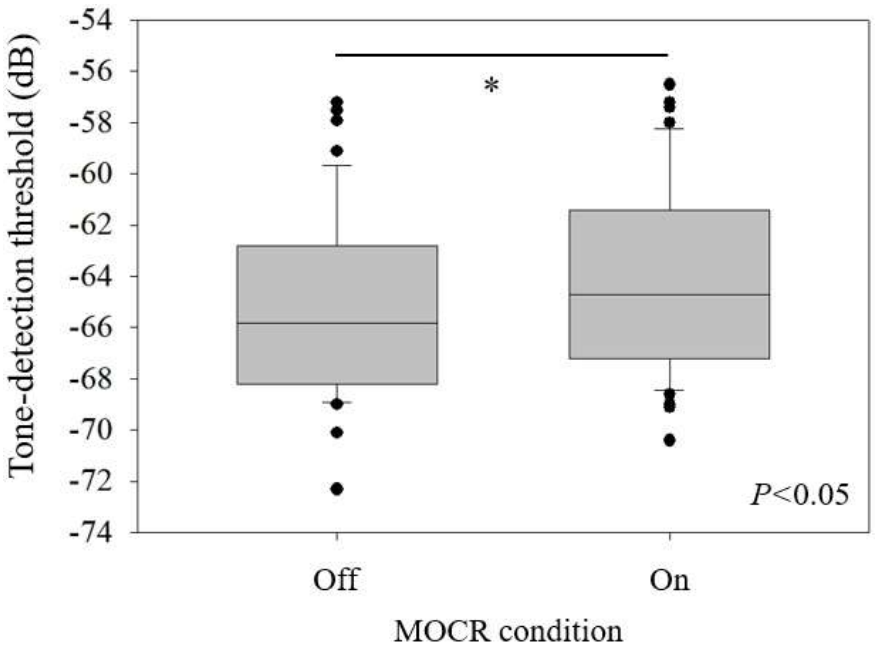

Figure 4-8. Tone-detection threshold for both MOCR off and on.
Box-and-whisker plot illustrating the median, interquartile range (shaded region), 1.5 x interquartile range (whiskers), and outliers (filled symbols) for tone-detection thresholds (dB) for both MOCR off and on conditions. Asterisks indicate a statistically significant difference at the $\alpha = 0.05$ level based on a paired-sampled *t*-tests**.**

Relationships Between Different MOCR Metrics

LLR latency shifts compared to OAE level shifts and threshold shifts

Figure 4-9 includes a series of scatterplots, each illustrating the relationship between the change in P1, N1, and P2 latency and the OAE-derived estimate of MOCR strength (change in OAE level between MOCR conditions, in dB) and tone-detection threshold (change in threshold level between MOCR conditions, in dB). None of the relationships were statistically significant ($p>0.05$).

LLR inter-amplitude shifts compared to OAE level shifts and threshold shifts

Figure 4-10 includes a series of scatterplots, each illustrating the relationship between P1-N1 and N1-P2 inter-amplitude (µV) and the OAE-derived estimate of MOCR strength (change in OAE level between MOCR conditions, in dB) and tone-detection threshold (change in threshold level between MOCR conditions, in dB). None of the relationships were statistically significant ($p>0.05$).

OAE level shifts compared to tone-detection threshold shifts

Figure 4-11 illustrates the relationship between tone-detection threshold (change in threshold level between MOCR conditions, in dB) and the OAE-derived estimate of MOCR strength (change in OAE level between MOCR conditions, in dB). The relationship was not statistically significant ($p>0.05$).

Summary of Findings

The primary objective of aim 1 was to examine the effect of MOCR activation on LLR amplitudes and latencies for a tone in quiet. The hypothesis was that LLR latencies would increase and amplitudes would decrease. This was informed by previous research from Billings (2009;2013) that demonstrated reduced LLR amplitudes and increased latencies as SNR decreases. **Table 4-4** presents descriptive statistics about the subjects, including age, gender, OAE with and without MOCR, and tone-detection with and without MOCR activation.

LLR Latency

- There was no significant difference in LLR latencies between MOCR off and on conditions.
- There was no relationship observed between LLR latency and tone-detection threshold.
- There was no relationship observed between the change in latency and OAE.

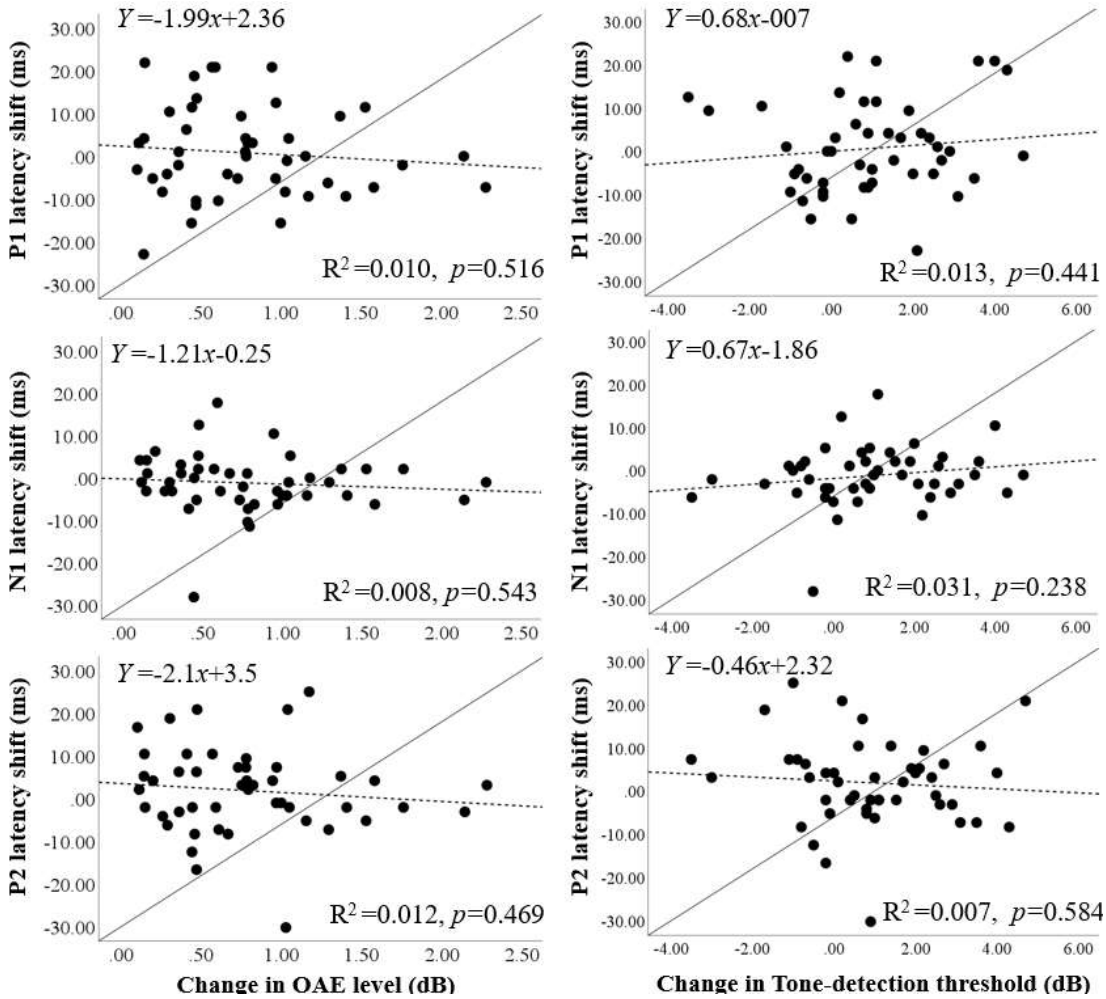

Figure 4-9. LLR latency shifts compared to OAE level shifts and thresholds shifts. Scatterplots illustrating the relationships between change in P1, N1, and P2 latency (ms) and OAE left shift (left) and tone-detection threshold shifts (right). The dashed line represents the linear regression, the solid line indicates a 1:1 relationship.

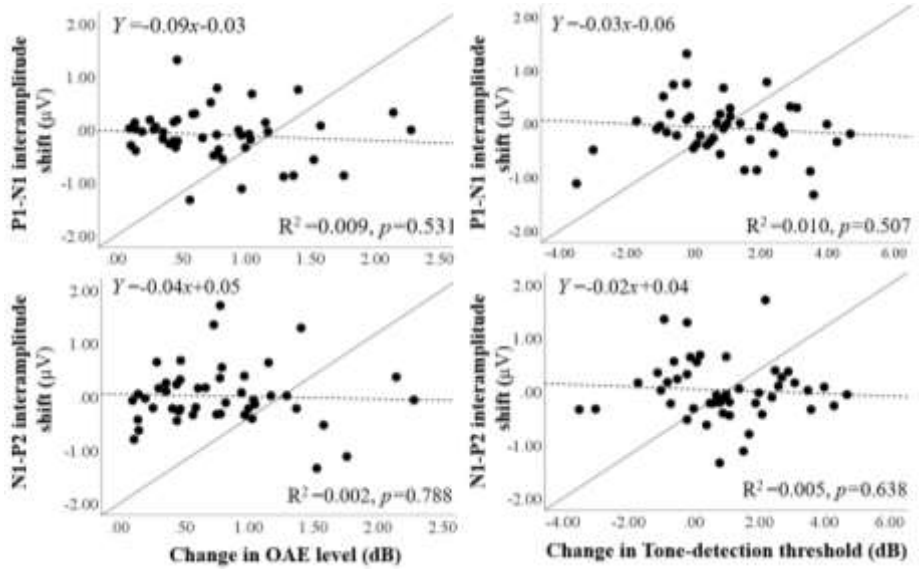

Figure 4-10. LLR inter-amplitude shifts compared to OAE level shifts and thresholds shifts.
Scatterplots illustrating the relationships between change in P1-N1 and N1-P2 inter-amplitude (μV) and OAE left shift (left) and tone-detection threshold shifts (right). The dashed line represents the linear regression, the solid line indicates a 1:1 relationship.

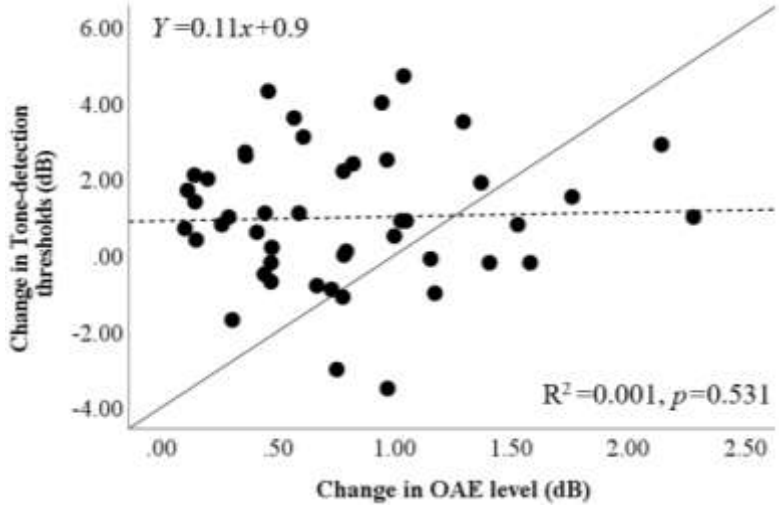

Figure 4-11. OAE level shifts compared tone-detection threshold shifts.
Scatterplots illustrating the relationships between OAE level shifts and tone-detection threshold shifts. The dashed line represents the linear regression, the solid line indicates a 1:1 relationship.

Table 4-4. Summary of subject with OAEs and tone-detection upon MOCR activation.

Subject (n)	Age	Gender	OAE MOCR	OAE No-MOCR	OAE Change	Tone-detection MOCR	Tone-detection No-MOCR	Tone-detection Change
A	19	F	9.1055	10.8652	1.7597	-61.4165	-62.9465	1.53
B	26	F	12.0051	13.532	1.5269	-66.6165	-67.4165	0.8
C	25	F	12.4373	13.2173	0.7799	-64.9165	-67.1165	2.2
D	20	F	17.6128	18.4349	0.8221	-63.7165	-66.1165	2.4
E	24	F	16.7366	16.8386	0.102	-68.0165	-68.7165	0.7
F	25	F	10.1045	11.3981	1.2936	-64.7165	-68.2165	3.5
G	27	F	9.7008	10.7278	1.027	-63.3165	-64.2165	0.9
H	29	F	8.5308	9.3136	0.7828	-59.8165	-59.8165	0
I	23	F	12.9794	14.3491	1.3697	-70.4165	-72.3165	1.9
J	23	F	5.3548	6.2993	0.9445	-58.3165	-62.3165	4
K	25	F	8.8062	9.536	0.7298	-64.9165	-64.0165	-0.9
L	25	F	11.5734	12.1823	0.609	-57.2165	-60.3165	3.1
M	36	F	14.5509	16.693	2.1422	-66.1165	-69.0165	2.9
N	20	F	18.7714	18.9705	0.1991	-66.2165	-68.2165	2
O	28	M	10.7427	11.0471	0.3043	-68.6165	-66.9165	-1.7
P	27	M	8.6494	9.8032	1.1538	-61.8165	-61.7165	-0.1
Q	26	F	13.5279	13.9725	0.4445	-64.7165	-65.8165	1.1
R	30	M	4.7918	5.2506	0.4588	-60.5165	-64.8165	4.3
S	24	F	10.1289	10.4891	0.3603	-66.2165	-68.9165	2.7
T	32	F	15.6058	17.1859	1.5801	-69.1165	-68.9165	-0.2
U	28	F	6.0431	6.4532	0.4101	-62.6165	-63.2165	0.6
V	31	F	15.5897	16.9956	1.4059	-63.6165	-63.4165	-0.2
W	29	F	10.3428	10.7847	0.4419	-58.0165	-57.5165	-0.5
X	23	F	13.1351	13.2481	0.113	-68.4165	-70.1165	1.7
Y	29	F	15.1591	16.1286	0.9695	-60.7165	-57.2165	-3.5

Table 4-4. (Continued).

Subject (n)	Age	Gender	OAE MOCR	OAE No-MOCR	OAE Change	Tone-detection MOCR	Tone-detection No-MOCR	Tone-detection Change
Z	23	F	9.4955	10.1623	0.6668	-67.5165	-66.7165	-0.8
AA	22	F	9.3058	9.875	0.5692	-60.3165	-63.9165	3.6
BB	22	F	15.3311	15.5909	0.2598	-65.5165	-66.3165	0.8
CC	23	F	8.2361	9.0287	0.7926	-68.4165	-68.5165	0.1
DD	27	M	18.8206	19.5727	0.7521	-64.9165	-61.9165	-3
EE	22	F	10.6228	10.9849	0.3621	-56.5165	-59.1165	2.6
FF	19	F	10.7663	10.9091	0.1428	-64.5165	-66.6165	2.1
GG	24	F	6.8195	7.5973	0.7777	-63.9165	-62.8165	-1.1
HH	19	F	14.5342	15.1246	0.5904	-67.5165	-68.6165	1.1
II	26	F	15.454	16.5029	1.0489	-61.7165	-62.6165	0.9
JJ	22	F	0.8212	0.7058	-0.1154	-67.0165	-66.4165	-0.6
KK	24	F	10.4405	11.6125	1.172	-69.0165	-68.0165	-1
LL	22	F	16.2753	16.7492	0.4739	-67.0165	-67.2165	0.2
MM	21	F	12.9665	13.4369	0.4704	-67.9165	-67.7165	-0.2
NN	29	F	5.9052	6.1946	0.2894	-62.0165	-63.0165	1
OO	21	F	6.6311	8.9107	2.2796	-67.2165	-68.2165	1
PP	22	F	11.0098	12.0084	0.9987	-57.4165	-57.9165	0.5
QQ	21	F	15.0617	15.532	0.4702	-65.6165	-64.9165	-0.7
RR	23	F	8.3642	9.3312	0.967	-62.0165	-64.5165	2.5
SS	24	F	10.5273	10.6726	0.1453	-58.8165	-60.2165	1.4
TT	25	M	7.2165	8.2547	1.0382	-60.2165	-64.9165	4.7
UU	28	F	13.1216	13.2713	0.1498	-67.9165	-68.3165	0.4

Note: OAE indicates sound pressure levels in dB SPL, while tone-detection indicates levels in dB.

LLR Inter-amplitude

- There was no significant difference in LLR inter-amplitudes between MOCR off and on conditions.
- There was no relationship observed between LLR inter-amplitude and tone-detection threshold.
- There was no relationship observed between the change in inter-amplitude and OAE.

Additional Analysis the relationship between different MOCR metrics

- There was no relationship observed between tone-detection threshold and the change in OAE.
- MOCR activation had a statistically significant effect on OAE level. OAE levels were reduced upon MOCR activation.
- MOCR activation had a statistically significant effect on tone-detection thresholds.
- Thresholds were increased (poorer) upon MOCR activation.

CHAPTER 5. EXPLORING SIGNAL-TO-NOISE RATIOS (SNRS) ENHANCEMENT THROUGH CAEP: INSIGHTS FROM THE AUDITORY EFFERENT SYSTEM IN A NOISEY ENVIRONMENT

Introduction

In the second experiment, a tone burst embedded in noise was presented to the subject's ipsilateral ear; noise was presented to the contralateral ear to activate the MOCR. The noise in the ipsilateral ear was presented at various levels to yield a range of SNRs. The research question was: Do CAEPs provide evidence of SNR improvement for a tone in noise during MOCR activation? The hypothesis was that CAEP amplitude increases and latency decreases during MOCR activation.

Figure 5-1 depicts the predicted effect of MOCR activation on Type I afferent auditory neuron rate-level functions in response to a tone presented in noise. The black solid line shows the rate-level function for a neuron in response to a tone in quiet without MOCR. Once the tone's sound level exceeds the neuron's threshold, the firing rate increases until the sound level reaches the neuron's saturation level. When the input level exceeds the neuron's saturation level, the firing rate of the auditory nerve does not change above the saturation firing rate. When a tone is presented in a background of noise, the rate level function changes and displays the three components of noise masking (indicated by the red line in the left panel). Firstly, the "line busy" effect of the noise results in an increase in the auditory neuron's background firing rate (Delgutte, 1990). The noise shifts the neuron's threshold to the level of the noise. As a result, the auditory neuron no longer responds to tone levels below the noise level, as the neuron is only responding to the noise. Secondly, the noise reduces the neuron's firing rate to tone levels above the noise due to two-tone suppression in the cochlea (Pang & Guinan, 1997). Thirdly, the noise causes a reduction in the firing rate of auditory neurons at high levels due to adaptation. The depletion of neurotransmitters in IHC contributes to adaptation (Boero et al., 2021). Consequently, noise limits the dynamic range of the neuron, potentially impacting signal detection. However, upon MOCR activation, the noise masking effect is reduced, as shown by the red dashed line in the left panel. The effect is that the output dynamic range of auditory nerve fibers is recovered (i.e., the rate-level function changes from the blue solid line to the red dashed solid line). This is called "MOCR-mediated unmasking", and it is supported by studies of auditory neuron rate-level functions (Winslow & Sachs, 1987; Winslow & Sachs, 1988; Kawase et al., 1993).

As an example of unmasking: without MOCR activation, the neuron firing to a 70-dB SPL tone is 130 spikes/sec, while the firing to the noise (30 dB SPL) is 65 spikes/sec. The firing rate to the tone is 65 spikes/sec higher than the firing rate to the noise without MOC. However, with MOC activation, the neuron's firing to the tone is 110 spikes/sec, but the neuron firing to the noise is reduced to 25 spikes/sec. The neuron's firing rate to the tone is 85 spikes/sec higher than the firing rate to the noise with MOC activation. Therefore, MOCR activation enhances the response to the tone relative to the response to the noise, resulting in an increase in SNR at the neural level.

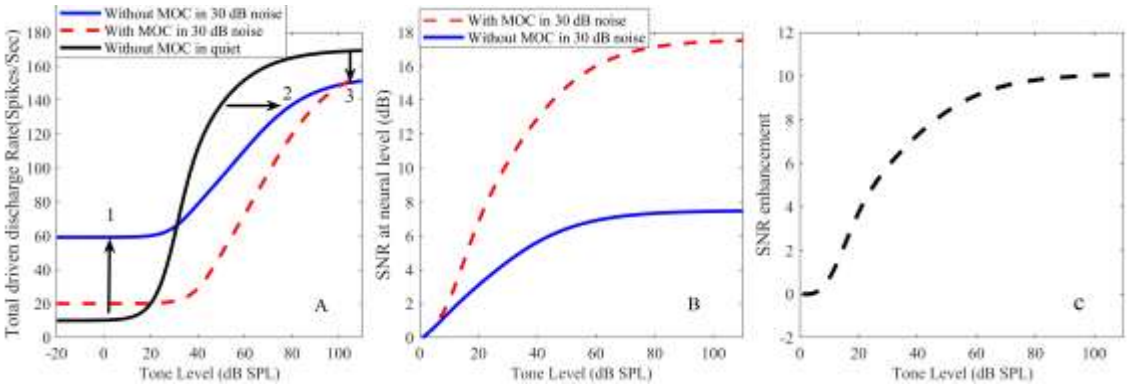

Figure 5-1. Schematic of the mid-spontaneous fiber rate-level function in quiet and noise with and without MOCR activation.

In the left panel, the black solid line indicates the neuron's rate level function in a quiet condition without MOC activation. The blue solid lines indicate the neuron's rate-level function in a background of 30 dB noise without MOC activation. The red dashed line indicates the neuron's rate-level function in a background of 30 dB noise with MOC activation. Each arrow indicates the effects of the three components of noise masking. In the middle panel, the blue solid line indicates SNRs at the neural level without MOC activation, whereas the red dashed line indicates SNRs at the neural level with MOC activation. SNR enhancement (shown in the right panel) is simply the difference in neural levels between MOCR activation and no MOCR activation.

The middle panel shows the estimated SNR at the neural level of a tone in a background of 30-dB SPL noise, with and without MOCR activation. For both MOCR conditions, SNR increases as the input level of the tone increases. However, when the MOCR is activated (see red dashed line), higher neural SNRs occur due to MOCR-mediated unmasking. The right panel shows the expected improvement in SNR resulting from MOCR-mediated unmasking. To compare how much the SNR increases during MOCR activation, we calculated the discharge rate of the neuron both with and without MOCR activation. These discharge rates were converted to dB and shown in the middle panel. The right panel presents the SNR enhancement as the difference between the MOCR activation and no MOCR activation for each discharge rate of the neurons.

As discussed, the LLR is sensitive to SNRs, as demonstrated in studies by Billings et al. (2009; 2013), where amplitude increases and latency decreases with increasing SNR. Hence, if MOCR activation leads to unmasking, we can expect certain changes to occur in the LLR. The hypothesis for this aim was that the amplitudes of the LLR increase and latencies decrease during MOCR activation due to the enhanced neural response to the tone relative to the no MOCR activation condition.

Methods

Subject

The subject and screening tests were the same as in Aim 1 and detailed in Chapter 4.

Cortical Auditory Evoked Potentials (CAEPs)

Equipment

The equipment was the same as in Aim 1and detailed in Chapter 4 (**Figure 5-2**).

Measurement conditions

The LLR was measured from the ipsilateral ear in response to 70-ms, 1-kHz alternating-polarity tone bursts (50-ms plateau and 10-ms rise/fall). Tone bursts were presented to the ipsilateral ear at a rate of 1.1/s and a level of 60 dB SPL. Tone bursts were combined with narrowband noise at various levels to yield a range of SNRs in the ipsilateral ear. Ipsilateral noise was centered at 1-kHz and had a ½-octave bandwidth. Noise levels included 35-, 45-, and 55-dB SPL to achieve SNRs of +25, +15, and +5 dB. For each SNR, the LLR was measured for MOCR active and MOCR inactive conditions. To activate the MOCR, white noise was presented to the contralateral ear at 60 dB SPL. The order of the MOCR conditions (i.e., active and inactive) and SNRs were randomized for each subject. To increase reliability and improve waveform morphology, LLR was

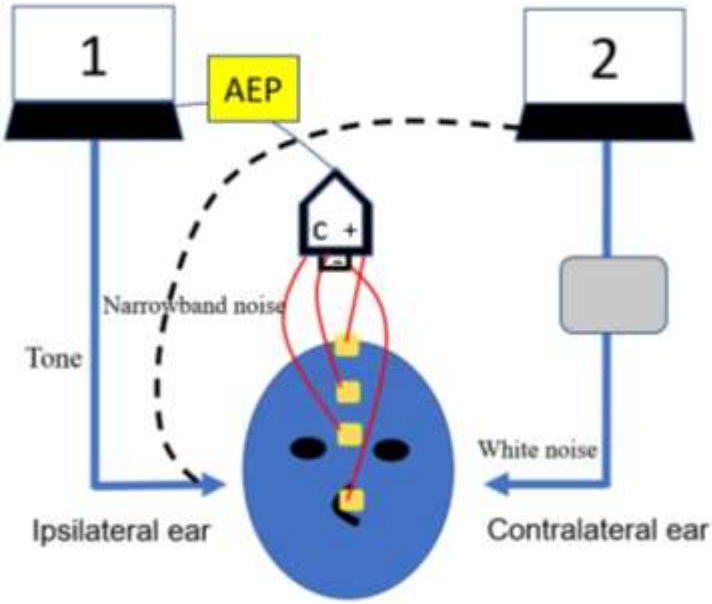

Figure 5-2. Experimental setup for CAEP in Aim 2.
The system involved the following steps: (1) the computer sent a 1-kHz tone to the ipsilateral ear via an insert earphone (Bio-logic) and recorded LLR, and (2) the computer provided white noise to the contralateral ear via ER3C insert earphone (Etymotic research). The gray box represents the function generator (Tektronix-AFG2021C), which was controlled by (2) the computer. It was utilized to generate noise and deliver it to the contralateral ear. The yellow box represents the AEP system used for recording LLR: c =ground, +=non-inverting electrodes, and -=inverting electrodes. The presence of the black dashed line indicates the ipsilateral noise (narrowband), which was controlled by (2) the computer. The ipsilateral noise is responsible for altering the SNRs. As a result, participants listened to a tone and noise in the ipsilateral ear. Four electrodes were attached to the participant's head, as in Aim 1.

measured for each MOCR condition at least 4 times using 200 sweeps per replication. In some cases, if the replications were inconsistent, a 5th replication was made and only the best 3 or 4 were included and averaged together in the final analysis.

Analysis

The analysis was the same as in Aim 1.

Statistical Analysis

The purpose of this analysis was to determine if MOCR activation and SNR have a significant effect on LLR inter-amplitudes and latencies. A repeated measures ANOVA was performed. Within-subject factors were MOCR condition (off and on) and SNR (5 dB, 15 dB, and 25 dB); an interaction term was also included but later dropped as it was not statistically significant. The dependent variables were LLR inter-amplitudes (P1-N1 and N1-P2) and latencies (P1, N1, and P2). A separate ANOVA was performed for each LLR component latency and amplitude. Post-hoc paired sample t-tests were conducted to compare the LLR inter-amplitude latency between MOCR off and at specific SNRs. Linear regression was also performed to examine relationships between the different MOCR metrics (neural, pre-neural, and behavioral assays).

Results

Aim 2 aimed to investigate the effect of MOCR in a noisy environment. The hypothesis proposed that the LLR component latencies decrease and inter-amplitude increase because the auditory efferent system provides an unmasking effect at the neural level, resulting in increased SNRs.

Effect of MOCR on LLR Latency Across the SNRs

A repeated measure ANOVA was conducted to investigate the effect of SNR and MOCR activation on LLR latency. In P1 latency, there was a statistically significant effect of MOCR, $F(1,46) = 15.552$, $p<0.001$, and SNRs, $F(1,46) = 60.072$, $p<0.001$. However, no significant interaction was observed between MOCR and SNRs, $F(1, 46) = 0.581$, $p=0.450$. In N1 latency, there was a statistically significant effect of MOCR, $F(1,44) = 14.828$, $p<0.001$, and SNRs, $F(1,44) = 136.287$, $p<0.001$. However, no significant interaction was observed between MOCR and SNRs, $F(1,44) = 2.170$, $p=0.148$. In P2 latency, there was a statistically significant effect of SNR, $F(1,45) = 62.387$, $p<0.001$. However, there was no statically significant effect of MOCR, $F(1,45) = 0.035$, $p=0.853$. Additionally, no significant interaction was observed between MOCR and SNRs, $F(1,45) = 0.965$, $p=0.331$.

Table 5-1 provides the means and SDs for the average of the P1, N1, and P2 across the SNRs. In P1 latency, the most significant reduction in latencies was observed at 15 dB, followed by 5 dB and 25 dB SNRs. All distributions were approximately normal based on the Shapiro-Wilk test ($p > 0.05$) across the SNRs. Post-hoc paired-sampled t-test were analyzed [P1 for MOCR off vs on at 5 dB SNRs: t(46) = 1.956 , p=0.057, P1 for MOCR off vs on at 15 dB SNRs: t(46) = 3.330, p=0.002, P1 for MOCR off vs on at 25 dB SNRs: t(46) = 1.624, p=0.111]. The latency reduction was only observed at 15 dB SNR, attributed to the increased SNR resulting from the unmasking effect.

In N1 latency, the greatest reduction in latencies was observed at 5 dB, followed by 15 dB and 25 dB SNRs. All distributions were approximately normal based on the Shapiro-Wilk test ($p > 0.05$). Post-hoc paired-sampled t-test were analyzed [N1 for MOCR off vs on at 5 dB SNRs: t(45) = 2.525, p=0.015, N1 for MOCR off vs on at 15 dB SNRs: t(46) = 2.373, p=0.022, N1 for MOCR off vs on at 25 dB SNRs: t(45) = 1.717, p=0.093]. The latency reduction was observed at both 5 dB and15 dB SNR, attributed to the increased SNR resulting from the unmasking effect.

In P2 latencies, the distributions at 25 dB SNR for both MOCR off and on, as well as at 15 dB SNR for MOCR on, were found to be approximately normal based on the Shapiro-Wilk test (p > 0.05). Post-hoc paired-sampled t-test were analyzed [P2 for MOCR off vs on at 5 dB SNRs: t(46) 0.550, p=0.585, P2 for MOCR off vs on at 15 dB SNRs: t(46) =-0.397, p=0.693, P2 for MOCR off vs on at 25 dB SNRs: t(45) =-0.848, p=0.401]. No unmasking effect was observed across any of the SNRs.

Figure 5-3 depicts the Box-and-whisker plot, illustrating the median P1 latency for both MOCR off and on conditions in the left panel, while the right panel displays the change in P1 latency across the SNRs. The plot includes the median, 1st- and 3rd-quartiles, 1.5×inter-quartile range, and outliers. The average P1 latency at 5dB SNR decreased from 91.27 ms for the MOCR-off condition to 87.27 for the MOCR-on condition – an average decrease of 3.85 ms. The average P1 latency at 15 dB SNR decreased from 82.41 ms for the MOCR-off condition to 77.49 for the MOCR-on condition – an average decrease of 4.92. The average of the P1 latency at 25 dB SNR decreased from 76.47 ms for the MOCR-off condition to 74.32 for the MOCR-on condition – an average decrease of 2.15 ms. In the right panel, the average change in P1 latency at 5 dB SNR was -3.85 (SD: 13.5), the change in P1 latency at 15 dB SNR was -4.92 (SD: 10.14), and the change in P1 latency at 25 dB SNR was -2.15 (SD: 9.07).

Figure 5-4 depicts the Box-and-whisker plot, illustrating the median N1 latency for both MOCR off and on conditions in the left panel, while the right panel displays the change in N1 latency across the SNRs. The plot includes the median, 1st- and 3rd-quartiles, 1.5×inter-quartile range, and outliers. The average N1 latency at 5 dB SNR decreased from 125.81 ms for the MOCR-off condition to 120.42 for the MOCR-on condition – an average decrease of 5.39 ms. The average N1 latency at 15 dB SNR decreased from 114.49 ms for the MOCR-off condition to 111.359 for the MOCR-on condition – an average decrease of 3.15. The average of the N1 latency at 25 dB SNR

Table 5-1. Summary of the LLR latency across the SNRs in Aim 2.

	Components					
	P1 latency (ms)		N1 latency (ms)		P2 latency (ms)	
SNRs	(MOCR off/on)		(MOCR off/on)		(MOCR off/on)	
5 dB	91.13 (15.21)/ 86.27 (14.61)	[-3.85]	125.81 (14.48)/ 120.42 (11.48)	[-5.39]	180.1 (26.9) / 178.86 (25.16)	[-1.24]
15 dB	82.41 (10.62)/ 77.49 (9.95)	[-4.92]	114.49 (8.88)/ 111.35 (9.14)	[-3.15]	167.43 (19.9)/ 168.63 (21.28)	[0.75]
25 dB	76.47 (11.62)/ 74.32 (12.08)	[-2.15]	109.56 (8.13)/ 107.78 (8.35)	[-1.79]	161.77 (16.98)/ 163.08 (16.12)	[1.32]

Note: SDs are indicated in parentheses. Change in latency between MOCR on and off are indicated in square brackets. Negative values indicate reduction latency.

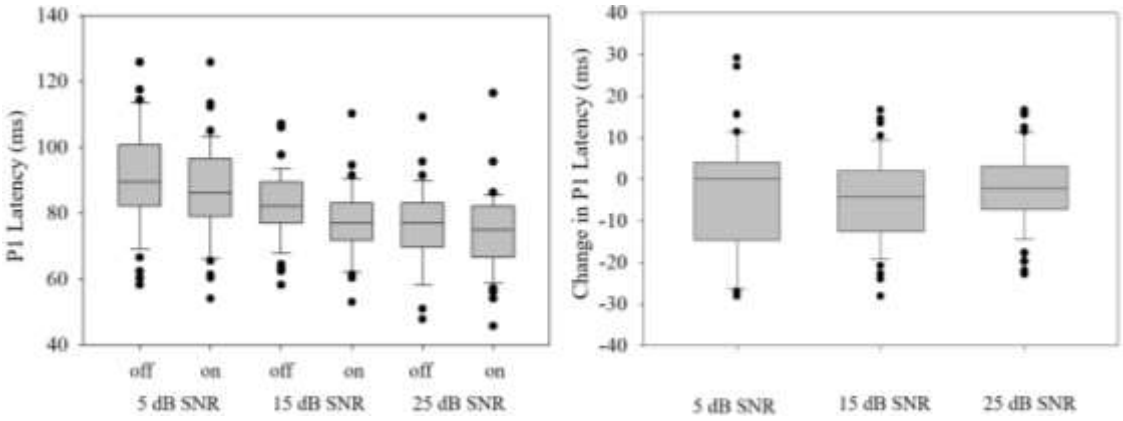

Figure 5-3. P1 for both MOCR off and on and latency shifts across the SNRs in Aim 2.

Box-and-whisker plot illustrating the median, interquartile range (shaded region), 1.5 x interquartile range (whiskers), and outliers (filled symbols) for P1 latency across the SNRs for both MOCR off and on conditions and for change in P1 latency across the SNRs.

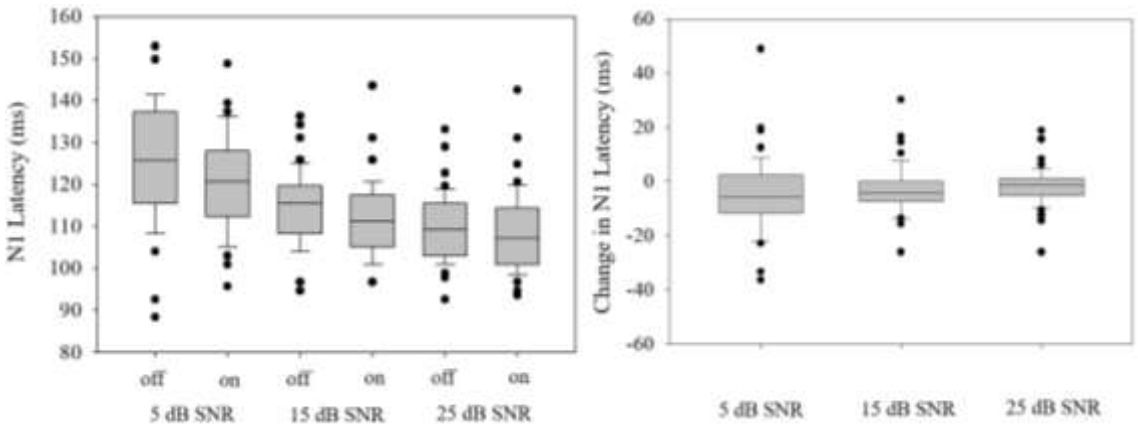

Figure 5-4. N1 for both MOCR off and on and latency shifts across the SNRs in Aim 2.

Box-and-whisker plot illustrating the median, interquartile range (shaded region), 1.5 x interquartile range (whiskers), and outliers (filled symbols) for N1 latency across the SNRs for both MOCR off and on conditions (left) and for change in N1 latency across the SNRs (right).

decreased from 109.56 ms for the MOCR-off condition to 107.77 for the MOCR-on condition – an average decrease of 1.79 ms. In the right panel, the average change in N1 latency at 5 dB SNR was -5.39 (SD: 14.47), the change in N1 latency at 15 dB SNR was -3.06 (SD: 9.16), and the change in N1 latency at 25 dB SNR was -1.79 (SD: 7.06).

Figure 5-5 depicts the Box-and-whisker plot, illustrating the median P2 latency for both MOCR off and on conditions in the left panel, while the right panel displays the change in P2 latency across the SNRs. The plot includes the median, 1st- and 3rd-quartiles, 1.5×inter-quartile range, and outliers. The average P2 latency at 5 dB SNR decreased from 180.1 ms for the MOCR-off condition to 178.86 for the MOCR-on condition – an average decrease of 1.24 ms. The average P2 latency at 15 dB SNR increased from 167.43 ms for the MOCR-off condition to 168.18 for the MOCR-on condition – an average increase of 0.75. The average of the P2 latency at 25 dB SNR decreased from 161.77 ms for the MOCR-off condition to 163.08 for the MOCR-on condition – an average decrease of 1.32 ms. In the right panel, the average change in P2 latency at 5 dB SNR was -1.38 (SD: 15.62), the change in P2 latency at 15 dB SNR was 0.79 (SD: 13.15), and the change in P2 latency at 25 dB SNR was 1.32 (SD: 13.01).

Effect of MOCR on LLR Inter-amplitude Across the SNRs

A repeated measure ANOVA was conducted to investigate the effect of SNR and MOCR activation for each inter-amplitude. In the P1-N1 inter-amplitude, there was a statistically significant effect of MOCR, $F(1,44) = 5.088$, $p=0.029$, and SNRs, $F(1,44) = 4.808$, $p<0.001$. However, no significant interaction was observed between MOCR and SNRs, $F(1, 44) = 0.001$, $p=0.972$. In the N1-P2 inter-amplitude, there was a statistically significant effect of MOCR, $F(1,44) = 12.781$, $p<0.001$, and SNRs, $F(1,44) = 80.052$, $p<0.001$. However, no significant interaction was observed between MOCR and SNRs, $F(1, 44) = 1.789$, $p=0.188$.

Table 5-2 provides means and SDs for the average of the P1-N1 and N1-P2 inter-amplitude (µV) across the SNRs. In the P1-N1 inter-amplitude (µV), the highest increment was observed at 25 dB, followed by 5 dB and 25 dB SNRs. All distribution were approximately normal based on the Shapiro-Wilk test ($p > 0.05$) except at 5 dB SNR for MOCR off ($p = 0.003$) and on ($p = 0.034$). Wilcoxon signed-rank test was analyzed [for MOCR off vs on at 5 dB SNR: $z = -1.475$, $p=0.140$]. Post-hoc paired-sampled *t*-test were analyzed for the P1-N1 inter-amplitude (µV) [for MOCR off vs on at 15 dB SNRs: $t(46) = -1.141$, $p=0.260$, for MOCR off vs on at 15 dB SNR: $t(45) = -1.445$, $p=0.155$]. No unmasking effect was observed across any of the SNRs. In the N1-P2 inter-amplitude (µV), the highest increment was observed at 5 dB, followed by 15 dB and 25 dB SNRs. All distribution were approximately normal based on the Shapiro-Wilk test ($p > 0.05$) except at 25 dB SNR for MOCR on ($p = 0.01$). Post-hoc paired-sampled *t*-test were analyzed for N1-P2 inter-amplitude (µV) [for MOCR off vs on at 5 dB SNR: $t(45) = -4.196$, $p<0.001$, for MOCR off vs on at 15 dB SNR: $t(46) = -2.363$, $p=0.022$]. Wilcoxon signed-rank test was analyzed [for MOCR off vs on at 25 dB SNR: $z = -1.076$, $p=0.282$].

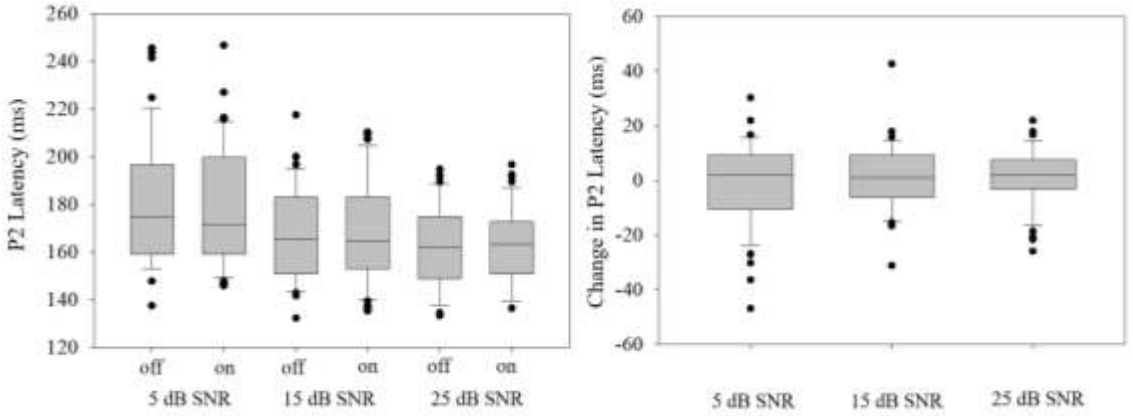

Figure 5-5. P2 for both MOCR off and on and latency shifts across the SNRs in Aim 2.

Box-and-whisker plot illustrating the median, interquartile range (shaded region), 1.5 x interquartile range (whiskers), and outliers (filled symbols) for P2 latency across the SNRs for both MOCR off and on conditions (left) and for change in P2 latency across the SNRs (right).

Table 5-2. Summary of the LLR inter-amplitude across the SNRs in Aim 2.

	Components			
	P1-N1 inter-amplitude (μV)		**N1-P2 inter-amplitude (μV)**	
SNRs	**(MOCR off/on)**		**(MOCR off/on)**	
5 dB	0.46 (0.33)/	[0.09]	0.57 (0.45)/	[0.31]
	0.55 (0.36)		0.88 (0.62)	
15 dB	0.79 (0.41)/	[0.06]	1.16 (0.81)/	[0.22]
	0.85 (0.44)		1.38 (0.77)	
25 dB	0.92 (0.52)/	[0.12]	1.74 (1.00)/	[0.13]
	1.04 (0.51)		1.86 (1.22)	

Note: SDs are indicated in parentheses. Change in each inter-amplitude (μV) between MOCR on and off are indicated in square brackets. Positive values indicate increment amplitude.

The inter-amplitude increment was observed at both 5 dB and 15 dB SNR, attributed to the increased SNR resulting from the unmasking effect.

Figure 5-6 depicts the Box-and-whisker plot, illustrating the median P1-N1 inter-amplitude (μV) for both MOCR off and on conditions in the left panel, while the right panel displays the change in P1-N1 inter-amplitude (μV) across the SNRs. The plot includes the median, 1st- and 3rd-quartiles, 1.5×inter-quartile range, and outliers. The average P1-N1 inter-amplitude (μV) at 5 dB SNR increased from 0.46 (μV) for the MOCR-off condition to 0.55 (μV) for the MOCR-on condition – an average increase of 0.09 ms. The average P1-N1 inter-amplitude (μV) at 15 dB SNR increased from 0.79 (μV) for the MOCR-off condition to 0.85 (μV) for the MOCR-on condition – an average increase of 0.06 ms. The average P1-N1 inter-amplitude (μV) at 25 dB SNR increased from 0.92 (μV) for the MOCR-off condition to 1.03 (μV) for the MOCR-on condition – an average increase of 0.11 ms. In the right panel, the average change in P1-N1 inter-amplitude (μV) at 5 dB SNR was 0.11 (SD: 0.43), the average change in P1-N1 inter-amplitude (μV) at 15 dB SNR was 0.06 (SD: 0.37), and the average change in P1-N1 inter-amplitude (μV) at 25 dB SNR was 0.13 (SD: 0.55).

Figure 5-7 depicts the Box-and-whisker plot, illustrating the median N1-P2 inter-amplitude (μV) for both MOCR off and on conditions in the left panel, while the right panel displays the change in N1-P2 inter-amplitude (μV) across the SNRs. The plot includes the median, 1st- and 3rd-quartiles, 1.5×inter-quartile range, and outliers. The average N1-P2 inter-amplitude (μV) at 5 dB SNR increased from 0.57 (μV) for the MOCR-off condition to 0.88 (μV) for the MOCR-on condition – an average increase of 0.3 ms. The average N1-P2 inter-amplitude (μV) at 15 dB SNR increased from 1.16 (μV) for the MOCR-off condition to 1.38 (μV) for the MOCR-on condition – an average increase of 0.22 (μV). The average N1-P2 inter-amplitude (μV) at 25 dB SNR increased from 1.74 (μV) for the MOCR-off condition to 1.86 (μV) for the MOCR-on condition – an average increase of 0.12 (μV). In the right panel, the average change in N1-P2 inter-amplitude (μV) at 5 dB SNR was 0.31 (SD: 0.49), the average change in N1-P2 inter-amplitude (μV) at 15 dB SNR was 0.22 (SD: 0.63), and the average change in N1-P2 inter-amplitude (μV) at 25 dB SNR was 0.13 (SD: 0.78).

Relationships Between Different MOCR Metrics

LLR latency shifts compared to OAE level shifts and threshold shifts across the SNRs

Figure 5-8 indicates a series of scatterplots, each illustrating the relationship between change in P1 latency across the SNRs and OAE level shifts (left) and change in tone-detection threshold (dB). In the left panel, the analysis revealed that there was no statistically significant relationship ($p > 0.05$) between the change in P1 latency at 5 dB SNR and 25 dB SNR and OAE level shifts. However, there was a negatively statistically significant ($p < 0.05$) relationship between the change in P1 latency at 15 dB SNR and MOCR strength. In the right panel, a statistically significant relationship ($p < 0.05$) was

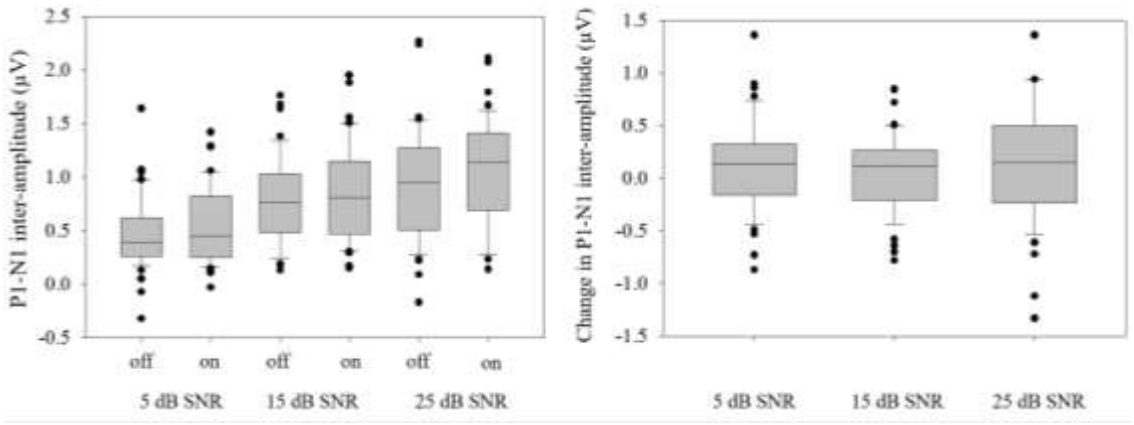

Figure 5-6. P1-N1 inter-amplitude for both MOCR off and on and latency shifts across the SNRs in Aim 2.

Box-and-whisker plot illustrating the median, interquartile range (shaded region), 1.5 x interquartile range (whiskers), and outliers (filled symbols) for P1-N1 inter-amplitude (μV) across the SNRs for both MOCR off and on conditions (left) and for change in P1-N1 inter-amplitude (μV) across the SNRs (right).

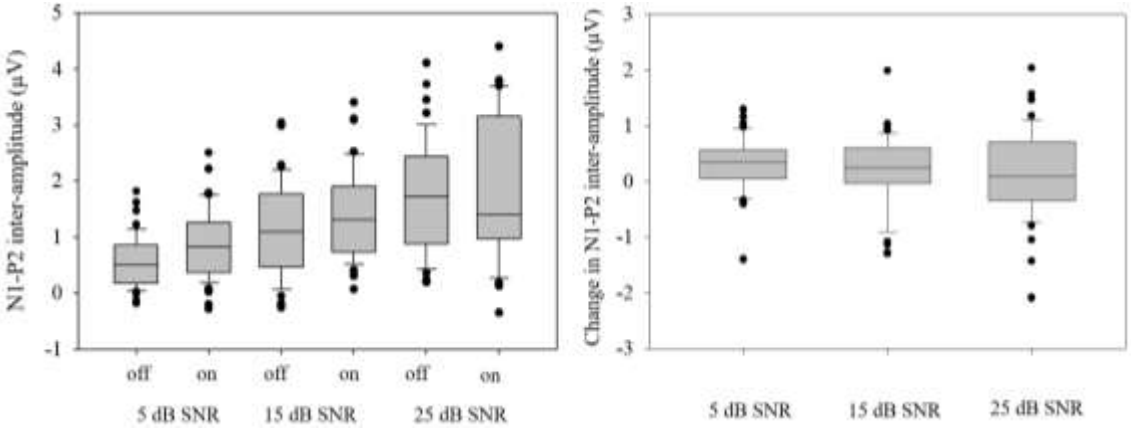

Figure 5-7. N1-P2 inter-amplitude for both MOCR off and on and latency shifts across the SNRs in Aim 2.

Box-and-whisker plot illustrating the median, interquartile range (shaded region), 1.5 x interquartile range (whiskers), and outliers (filled symbols) for N1-P2 inter-amplitude (μV) across the SNRs for both MOCR off and on conditions (left) and for change in N1-P2 inter-amplitude (μV) across the SNRs (right).

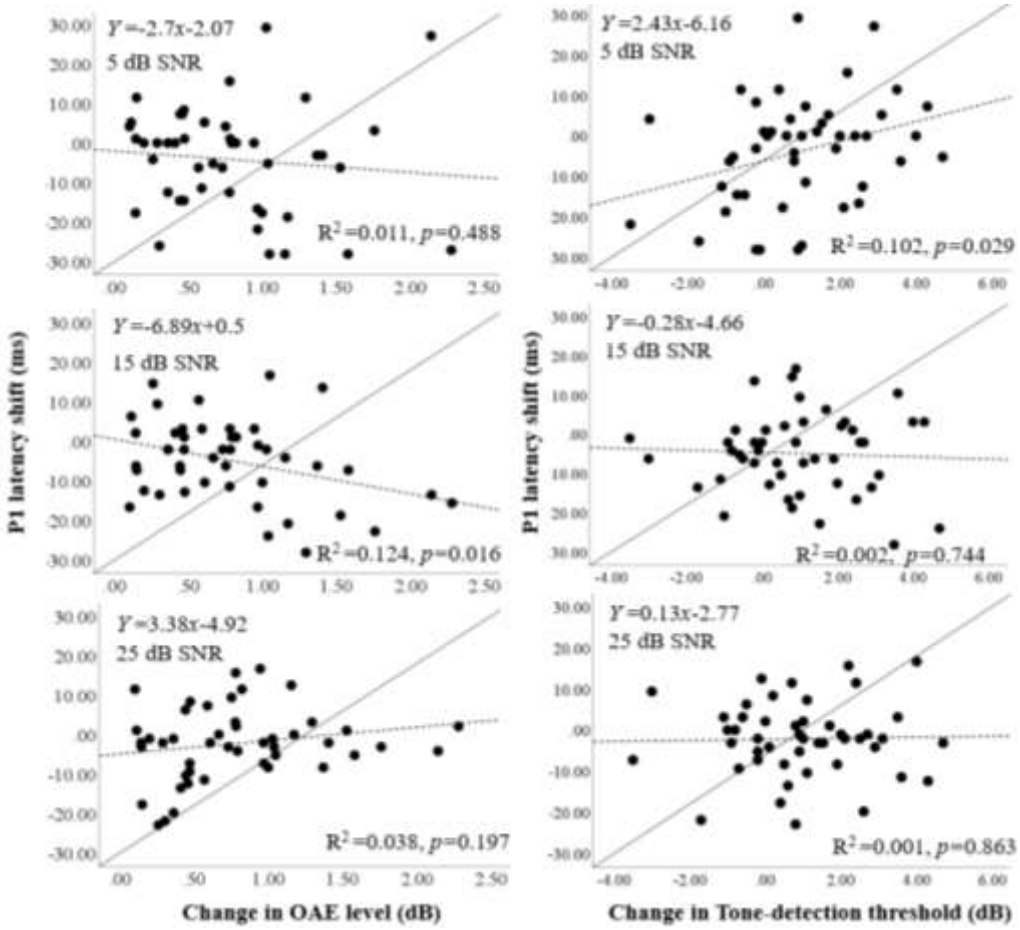

Figure 5-8. P1 latency shifts compared to OAE level shifts and threshold shifts across the SNRs in Aim 2.

Scatterplots illustrating the relationships between change in P1 latency and OAE level shift (left) and change in tone-detection threshold (dB). The dashed line represents the linear regression, the solid line indicates a 1:1 relationship.

observed between changes in P1 latency at 5 dB SNR and changes in tone-detection threshold for all components. However, no relationship was found at 15 dB SNR and 25 dB SNR ($p > 0.05$).

Figure 5-9 indicates a series of scatterplots, each illustrating the relationship between change in N1 latency across the SNRs and OAE level shifts (left) and change in tone-detection threshold (dB). In the left panel, there was no statistically significant relationship ($p > 0.05$) observed between change in N1 latency and OAE level shifts across the SNRs. In the right panel, there was no statistically significant relationship ($p > 0.05$) between the change in N1 latency and tone-detection threshold shifts across all SNRs.

Figure 5-10 indicates a series of scatterplots, each illustrating the relationship between change in P2 latency across the SNRs and OAE level shifts (left) and change in tone-detection threshold (dB). In the left panel, there was no statistically significant relationship ($p > 0.05$) observed between change in P2 latency and OAE level shifts across the SNRs. In the right panel, there was no statistically significant relationship ($p > 0.05$) between the change in P2 latency and tone-detection threshold shifts across all SNRs.

LLR inter-amplitude shifts compared to OAE level shifts and threshold shifts across the SNRs

Figure 5-11 indicates a series of scatterplots, each illustrating the relationship between change in P1-N1 inter-amplitude across the SNRs and OAE level shifts (left) and change in tone-detection threshold (dB). In the left panel, there was no statistically significant relationship ($p > 0.05$) observed between change in P1-N1 inter-amplitude and OAE level shifts across the SNRs except at 25 dB SNR ($p = 0.014$). In the right panel, there was no statistically significant relationship ($p > 0.05$) between the change in P1-N1 inter-amplitude and tone-detection threshold shifts across all SNRs.

Figure 5-12 indicates a series of scatterplots, each illustrating the relationship between change in N1-P2 inter-amplitude across the SNRs and OAE level shifts (left) and change in tone-detection threshold (dB). In the left panel, there was no statistically significant relationship ($p > 0.05$) observed between change in P1-N1 inter-amplitude and OAE level shifts across the SNRs except at 25 dB SNR ($p = 0.029$). In the right panel, there was no statistically significant relationship ($p > 0.05$) between the change in N1-P2 inter-amplitude and tone-detection threshold shifts across all SNRs.

Summary of Findings

The primary aim of the study was to examine the effect of MOCR activation on LLR amplitudes and latencies for a tone in noise. The hypothesis was that LLR latencies would decrease and amplitudes would increase.

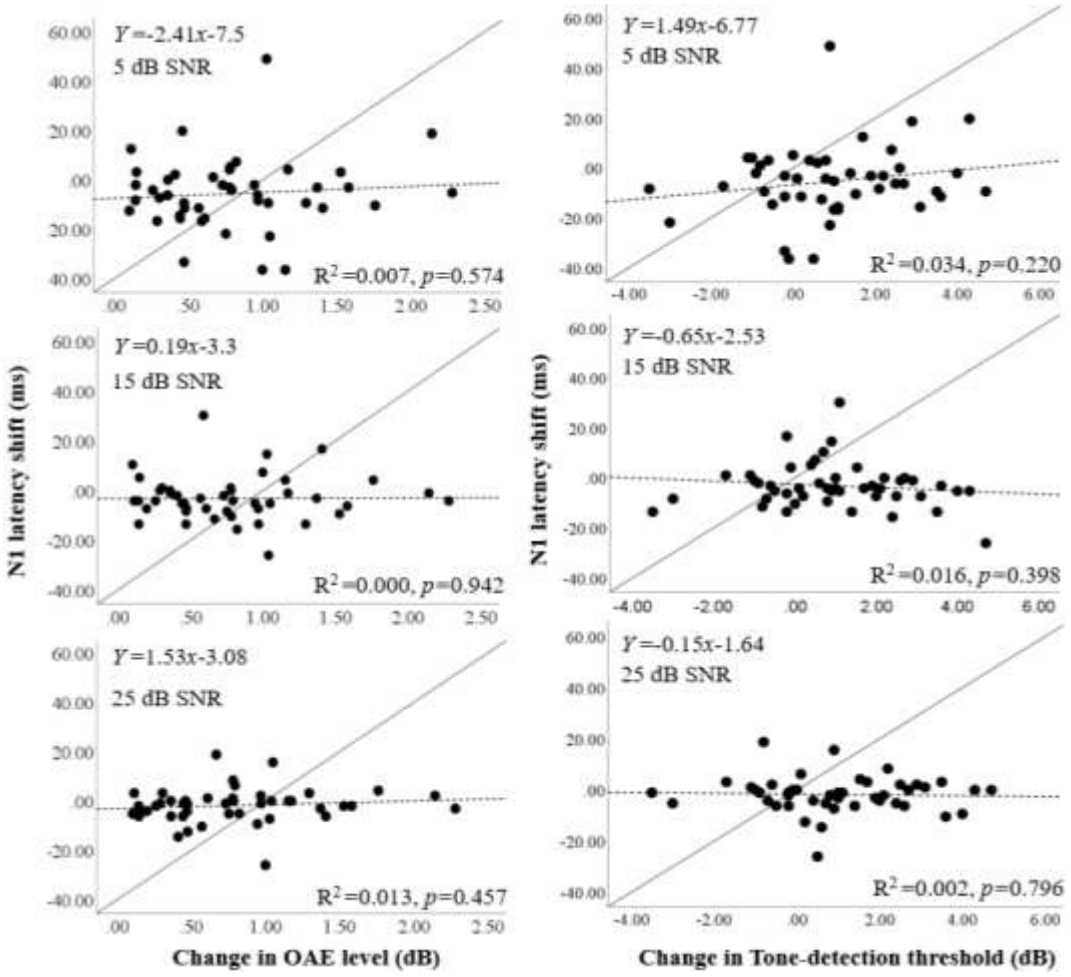

Figure 5-9. N1 latency shifts compared to OAE level shifts and threshold shifts across the SNRs in Aim 2.

Scatterplots illustrating the relationships between change in N1 latency and OAE level shift (left) and change in tone-detection threshold (dB). The dashed line represents the linear regression, the solid line indicates a 1:1 relationship.

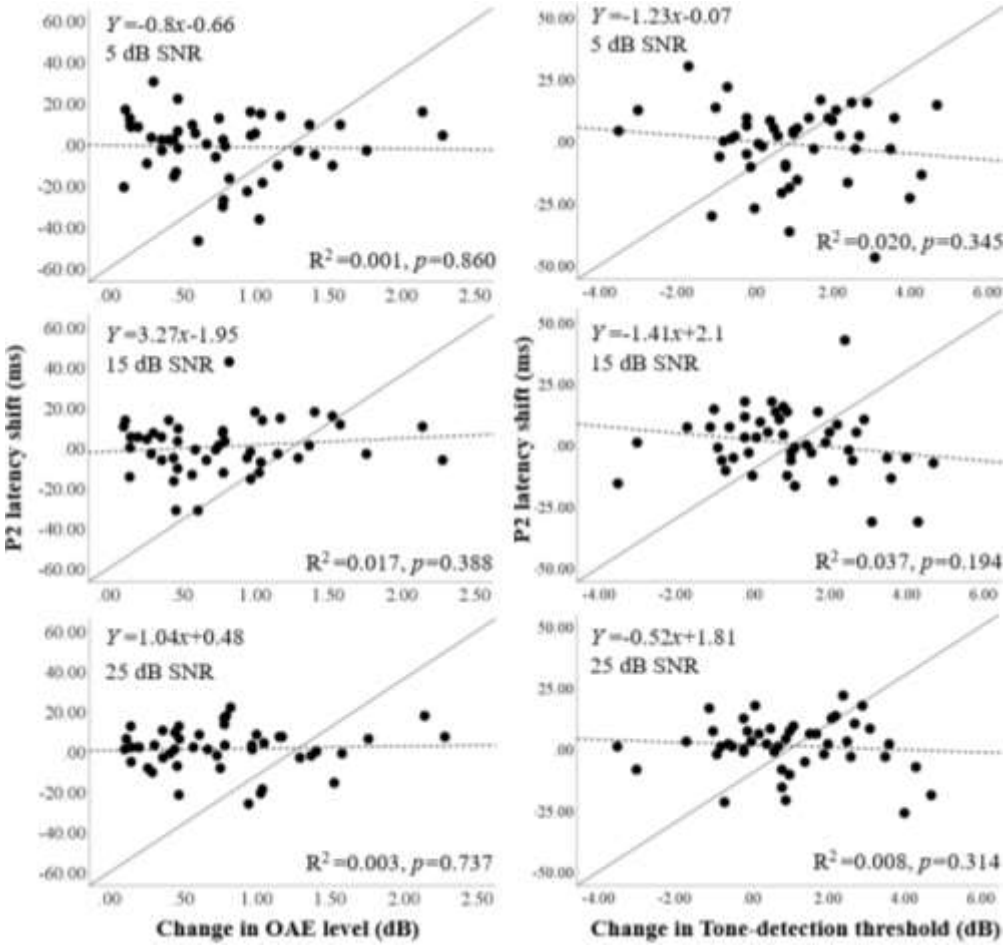

Figure 5-10. P2 latency shifts compared to OAE level shifts and threshold shifts across the SNRs in Aim 2.

Scatterplots illustrating the relationships between change in P2 latency and OAE level shift (left) and change in tone-detection threshold (dB). The dashed line represents the linear regression, the solid line indicates a 1:1 relationship.

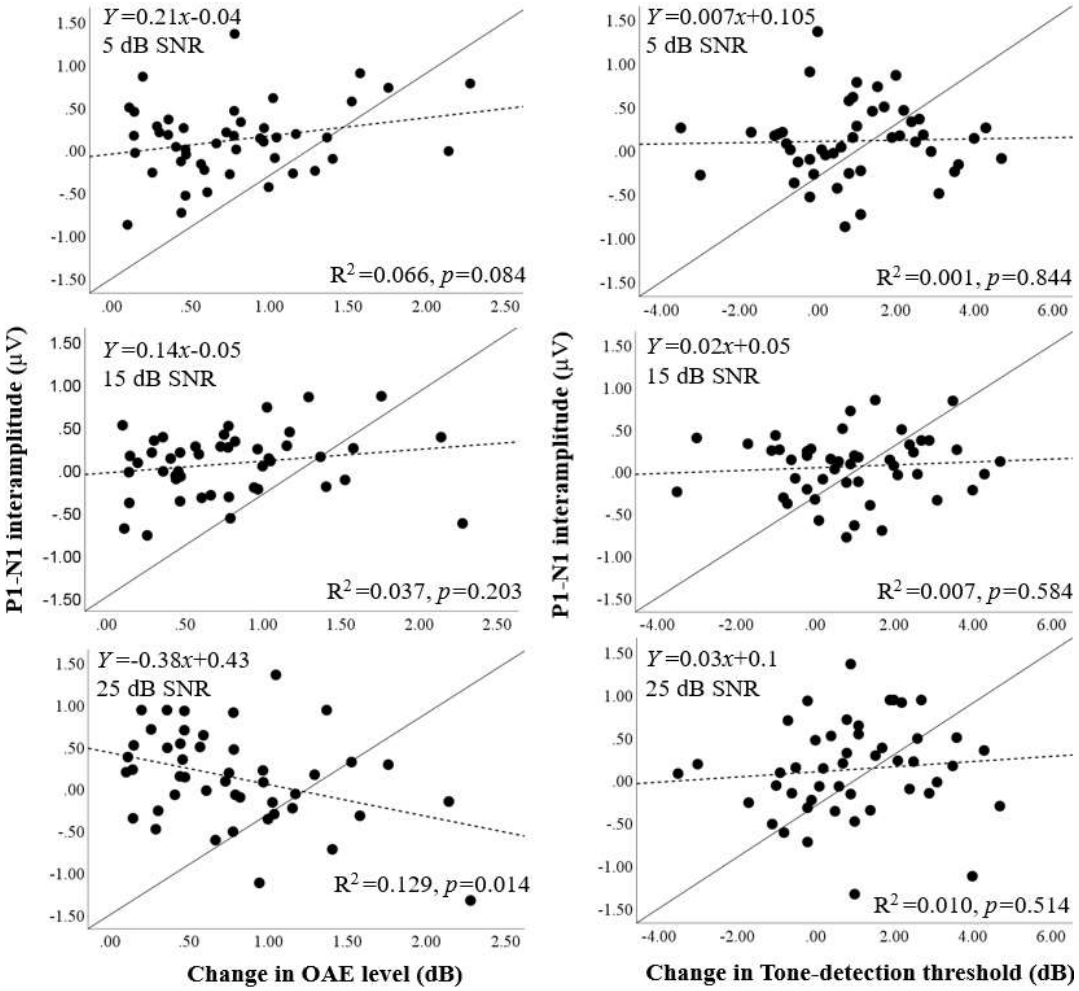

Figure 5-11. P1-N1 inter-amplitude shifts compared to OAE level shifts and thresholds shifts across the SNRs in Aim 2.
Scatterplots illustrating the relationships between change in P1-N1 inter-amplitude and OAE level shift (left) and change in tone-detection threshold (dB). The dashed line represents the linear regression, the solid line indicates a 1:1 relationship.

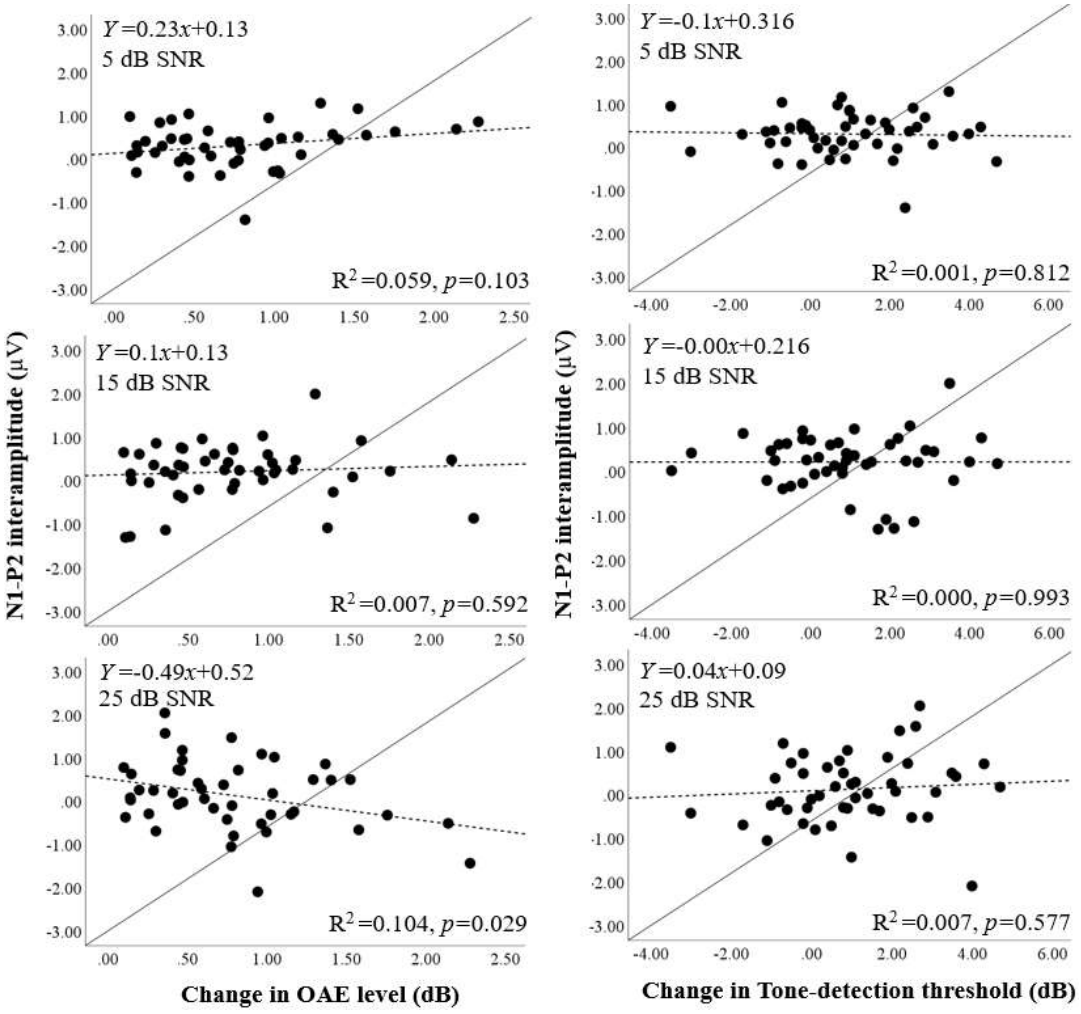

Figure 5-12. N1-P2 inter-amplitude shifts compared to OAE level shifts and thresholds shifts across the SNRs in Aim 2.
Scatterplots illustrating the relationships between change in N1-P2 inter-amplitude and OAE level shift (left) and change in tone-detection threshold (dB). The dashed line represents the linear regression, the solid line indicates a 1:1 relationship.

LLR Latency

- In P1 latency, there was a statistically significant effect of MOCR and SNR.
- In N1 latency, there was a statistically significant effect of MOCR and SNR.
- In P2 latency, there was no statistically significant effect of MOCR, but there was a statistically significant effect of SNR.
- There was no correlation with OAE level shifts, except at15 dB SNR, and tone-detection threshold shifts, except 5 dB SNR.
- There was no correlation with OAE level shifts and tone-detection threshold shifts.
- There was no correlation with OAE level shifts and tone-detection threshold shifts.

LLR Inter-amplitude

- In the P1-N1 inter-amplitude, there was a statistically significant effect of MOCR and SNR.
- In the N1-P2 inter-amplitude, there was a statistically significant effect of MOCR and SNR.
- There was no correlation with OAE level shifts, except 25 dB SNR, and tone-detection threshold shifts.
- There was no correlation with OAE level shifts, except 25 dB SNR, and tone-detection threshold shifts.

CHAPTER 6. DISCUSSION

The Effect of the Auditory Efferent System on Neural Encoding of a Tone in Quiet

In the first aim, a tone burst was delivered to the subject's ipsilateral ear, accompanied by quiet environment, while noise was presented to the contralateral ear to activate the MOCR. This study examined CAEP during MOCR activation in a quiet environment, with an expectation of decreased SNR resulting from reduced cochlear amplification. As a result, the study predicted a reduction in CAEP amplitude and an increase in latency.

Findings demonstrated that MOCR activation did not have a significant effect on either LLR latency or inter-amplitudes. Latency did increase by 0.64 and 1.88 for P1 and P2, respectively, but decreased by 1.22 ms for N1. However, these changes were not statistically significant. Additionally, there were small amplitude reductions of 0.09 in P1-N1 and 0.025 in N1-P2 when the MOCR was activated, however, the changes were not significant. Overall, the lack of MOCR effects on LLR latencies and inter-amplitudes fail to substantiate the hypothesis.

Several previous studies have also failed to identify a significant effect of the MOCR on evoked potential latencies for potentials originating from the brainstem and higher. Holtmann et al. (2023) investigated the effect of MOCR activation on auditory brainstem response (ABR) waves III and V and found no significant latency difference between MOCR conditions. However, Matas et al. (2010) found a statistical difference for ABR latency and amplitude. This observation may imply that the impact of the auditory efferent system is evident at the neural level (i.e., in cortical potentials), potentially due to a lack of effect at more peripheral neural levels. Using peripheral neural assays of the MOCR, several studies using CAP (Lichtenhan et al., 2016; Najem et al., 2016), have reported a decrease in CAP inter-amplitudes upon MOCR activation. Thus, there is evidence that the MOCR does influence early neuronal processes. Desmedt (1962) confirmed a reduction in amplitude when the efferent system is activated, specifically measuring the overall response from the cochlear to the auditory cortex. Furthermore, Rao et al. (2020) also validated a decrease in P300 amplitude and an increase in latency. While these studies align with our hypotheses, our present findings are not in accord. The utilization of contralateral acoustic stimulation in the current aim1 follows a similar methodology, yet the obtained results present conflicting outcomes. These discrepancies may be attributed to the following factors.

One factor that may have impacted findings is the duration of the measurement sessions. To enhance confidence in LLR component identification, each condition was measured between four and five times, resulting in a time range of 12 to 20 minutes for each stimulus condition in LLR. However, it is important to acknowledge that conducting the measurement over such an extended period may potentially diminish the MOCR effect. In a recent study, Holtmann et al. (2023) examined the effect of MOCR activation on ABR amplitude and found that the MOCR effect weakened as the study duration

increased. Consequently, any MOCR effect impacting the late neural response may also become weaker over repeated measurement. To resolve this issue, a suitable rest period should be incorporated during the study, and the possibility of conducting the study with two visits instead of one can be explored. Another possible explanation for the lack of MOCR effect is that the reduction in cochlear output upon MOCR activation is compensated by central gain. Central gain is a compensatory mechanism thought to offset reduced peripheral output, as may occur because of hearing loss or, perhaps, MOCR activation. The phenomenon of auditory central gain reveals an increase in gain in higher areas leading towards the auditory cortex (reviewed by Auerbach et al., 2014). Upon closer examination, it was observed that the response of the auditory nerve and cochlear nucleus did not exhibit compensation despite the increase in sound intensity. However, gain effects were observed in the inferior colliculus and auditory cortex when high intensities were administered. This gain phenomenon is not universal across all auditory systems, and it has been particularly observed close to the auditory cortex, especially in response to louder sounds. Therefore, drawing from this study, it can be inferred that when the MOCR is activated, the diminished output from the cochlea is compensated by an increase in central gain near the auditory cortex. Sun et al. (2008) conducted a study in which they assessed ABR threshold shift and gene microarray to see auditory cortex amplitude change of rats exposed to noise. The objective of this study was to measure threshold shift and amplitude change of the auditory cortex in response to noise and validate the presence of central gain. While there was a slight variance observed across frequencies, the amplitude of the auditory cortex significantly altered after 4 hours of noise exposure compared to pre-exposure levels. However, after one day, the measured value recovered and returned to a similar level as before the noise exposure. Therefore, it provides evidence that decreases in cochlear output result in increase in amplitude response within the auditory cortex. Bramhall and his colleagues (2020) studied central auditory gain through noise-induced reduced ABR amplitude in young veterans with normal hearing. To provide an overall response, the entire response waveform area was analyzed. Interestingly, the veteran group with a low middle latency response (MLR) area showed a higher LLR area than the non-veteran. Greater responses were observed in N1 and P2. This provides evidence of greater gain compensation in regions closer to the auditory cortex.

Although a significant main effect of MOCR activation on the LLR was not found, there were individual subjects who exhibited the predicted changes in LLR amplitudes and latencies. Approximately 50% of the attendees showed an increase in latency and/or a decrease in inter-amplitude; however, this was not sufficient to detect a significant main effect of the MOCR on LLR metrics. In conclusion, the results did not align with our hypotheses, as not all participants exhibited the expected outcomes of increased latency and decreased inter-amplitude. This underscores the necessity for further research in this area.

The Effect of the Auditory Efferent System on Neural Encoding of a Tone Across the SNRs in Noise

In the second aim, a tone burst was delivered to the subject's ipsilateral ear, embedded in background noise, while noise was presented to the contralateral ear to activate the MOCR. This study examined CAEPs evoked by tones in noise during MOCR activation, with an expectation of an increased SNR due to a MOCR-mediated unmasking effect. As a result, the study observed an increase in CAEP inter-amplitude and a reduction in latencies, as we hypothesized.

Billings et al. (2009; 2013) investigated the relationship between SNR and LLR, showing a decrease in latency and an increase in amplitude with increasing SNR. Billings and Grush (2016) examined the CAEP in relation to signal type and SNR, revealing that as the SNR decreased, there was a noticeable increase in latency for P1, N1, and P2 components. Notably, speech signals exhibited even greater latency compared to other signal types. These studies provide evidence of CAEP sensitivity to SNR. However, whereas previous studies-controlled SNR by directly manipulating the noise in the ear canal, our aim was to utilize CAEPs to detect MOCR-mediated unmasking and SNR enhancement at the neural level.

In the absence of MOCR activation, the current findings agree with those of Billings et al. (2009) and others. Specifically, as the ipsilateral noise was increased to achieve poorer SNRs, latencies increased and inter-amplitudes decreased. This pattern of changes also occurred during MOCR activation. These findings align with the trends observed in the Billing study (2009), suggesting a greater effect of SNR on cortical auditory evoked potentials at low SNR. For instance, in the case of N1, the transition from -10 to 0 dB SNR resulted in an approximate 50 ms reduction, whereas the transition from 0 to 10 dB SNR only caused a mere 10 ms reduction. Similarly, for P1, which exhibited less variability in latency compared to other measurements, there was a 20 ms reduction when transitioning from -10 to 0 dB SNR, and a 10 ms reduction when transitioning from 0 to 10 dB SNR. Data provide evidence of higher latency adjustments, indicative of more gain at lower SNR levels.

For a fixed SNR, MOCR activation resulted in a decrease in latency for P1 and N1. This decrease may be attributed to the expected unmasking effect resulting in an increased SNR. There was no significant MOCR effect on P2 latency. The reason for lack of a significant MOCR effect on P2 is unclear. However, P2 tended to exhibit poorer morphology compared to the earlier latency components, suggesting that it may be more vulnerable to noise or influenced by artifacts from prolonged measurements. Additionally, P2 is the most impacted by arousal and attention. This was especially the case for the +5 dB SNR, resulting in certain measurements being excluded from analysis due to lack of confidence in identifying P2. N1 displayed the best morphology of the difference LLR components and was identifiable at all SNR conditions, with and without MOCR activation. N1 serves as a reliable indicator of hearing sensitivity (Davis et al., 1967) and is trusted due to its association with speech perception (Parbery-Clear et al., 2011; Billings et al., 2013). Moreover, the influence of central gain suggests that the

higher auditory system may also impact N1. The lack of a statistically-significant interaction between SNR and MOCR is consistent with MOCR unmasking at all SNRs.

Concerning the effect of MOCR activation on LLR inter-amplitudes: For a fixed SNR, MOCR activation increased both the P1-N1 and N1-P2 inter-amplitudes. These increases in amplitude may be attributed to the expected unmasking effect resulting in an increased SNR. It is worth noting that both SNR and MOCR independently exert a significant effect on latency and inter-amplitude, with no interaction found between SNR and MOCR. However, we were able to demonstrate the enhancement of SNR through unmasking, achieved by reductions in latency and increases in inter-amplitude measures. The lack of a statistically-significant interaction between SNR and MOCR is consistent with MOCR unmasking at all SNRs.

Furthermore, the study investigated the effect of the SNRs on latency and inter-amplitude variations, referred to as SNR benefit. Regarding P1 latency, an average reduction of 8.3 ms was observed when the SNR increased from 5 dB to 15 dB, while an average reduction of 4.6 ms occurred with an SNR change from 15 dB to 25 dB. For N1 latency, there was an average decrease of 10.2 ms when increasing the SNR from 5 dB to 15 dB, and a decrease of 4.3 ms when increasing it from 15 dB to 25 dB. In the case of P2 latency, a decrease of 11.5 ms was observed with an SNR increase from 5 dB to 15 dB, and a decrease of 5.6 ms was observed when increasing the SNR from 15 dB to 25 dB. These results clearly demonstrate that latency decreases as the SNR increases. Notably, the SNR effects on latencies were more pronounced at lower SNR levels. Regarding the P1-N1 inter-amplitude, there was an average increase of 0.32 when the SNR increased from 5 dB to 15 dB. Furthermore, when the SNR changed from 15 dB to 25 dB, the average increase was 0.16. As for the N1-P2 inter-amplitude, there was an average increase of 0.55 when the SNR increased from 5 dB to 15 dB, and an increase of 0.53 when increasing the SNR from 15 dB to 25 dB. Notably, like latency, the SNR effects was more pronounced at lower SNR levels.

Additionally, the investigation focused on the extent of SNR increase caused by MOCR activation. Evidence of an increase in SNR resulting from the MOCR effect was observed for P1 and N1 latencies, as they decreased with MOCR activation. These decreases can be related to a specific amount of SNR enhancement. To determine the improvement in SNRs achieved through MOCR activation, we relate the change in latency (or amplitude) across a fixed 10 dB SNR increase in the absence of MOCR activation, to the change in latency (or amplitude) to an unknown SNR increase in the presence of MOCR activation. Using cross-multiplication, the unknown SNR increase is calculated. Upon MOCR activation, the average SNR at P1 latency increased by 6.2 dB. At N1 latency, the average SNR also increased by 4.3 dB. The P1-N1 inter-amplitude showed an increase of 3.4 dB SNR, while the N1-P2 inter-amplitude exhibited an average increase of 2.2 dB SNR. These results confirm the latency's significant SNR benefit following MOCR activation.

In Aim 2, we demonstrated how MOCR-mediated unmasking contributes to enhanced SNRs by reducing LLR latency and increasing LLR inter-amplitude.

Unmasking has the potential to enhance human speech perception in noisy environments, shedding light on the underlying reasons for individual variations in speech perception abilities in noise. While previous studies have primarily focused on manipulating noise and signal characteristics to improve speech perception, our study offers a physiological perspective that elucidates the impact of the unmasking effect on speech perception abilities in noise.

Relationship Between Different MOCR Metrics

The present study included 3 assays of the MOCR: an OAE-based pre-neural assay, and tone-detection behavioral assay, and the LLR-based neural assay. Activation of the MOCR through contralateral acoustic stimulation significantly reduced OAE amplitude and elevated tone-detection threshold. This outcome aligns with our expectations, indicating that the activation of the MOCR leads to a reduction in cochlear amplification, thereby resulting in a decreased SNR.

In aim 1, no correlation was identified among latency shifts of the LLR, OAE levels, and threshold shifts. Similarly, no association was found in the inter-amplitudes of P1-N1 and N1-P2. Regarding aim 2, there were several instances of a significant correlation between MOCR metrics from the different assays; however, there was not a consistent pattern across either SNR or LLR components.

The absence of consistent associations across MOCR assays may be attributed, in part, to the usage of non-identical stimuli and tasks. While a 1 kHz tone was utilized in all tests, the stimuli used to elicit OAE, tone-detection thresholds, and CAEPs varied. These differences may have weakened the size of the MOCR effect in each study, consequently impacting the strength of potential associations. Specifically, in the case of CAEP, employing a higher sound level resulted in a larger waveform, offering a potential solution to counterbalance the limitations posed by poor waveforms observed in some subjects. Despite the absence of correlation, the MOCR effect was observed consistently across all studies. Furthermore, in our current study, since the tone-detection investigation engaged the MOCR under quiet conditions, conducting the tone-detection study in a noisy environment could potentially introduce another correlation.

To activate the MOCR, we utilized 60 dB SPL white noise. Despite the identical conditions, the intensity of the stimuli used to induce OAE, elicit auditory evoked responses, and measure thresholds differed. Consequently, while the conditions for reducing cochlear amplification through MOCR activation remained consistent, the evoked intensity at each auditory location may have varied. Furthermore, there were discrepancies in the study duration. OAE measurements took approximately 5 minutes, while tone-detection required around 40 minutes. However, in the case of LLR, measurements were combined for both aim 1 (with and without contralateral acoustic stimulation) and aim 2 (with and without contralateral acoustic stimulation across the SNRs). Essentially, aim 1 also took approximately 2 hours. The order of aim 1 measurements varied among subjects, with some undergoing the measurements first and

others last. This discrepancy in the timing of measurements can potentially diminish the MOCR effect over time and introduce high artifacts. As a result, it could pose limitations in accurately assessing the strength of MOCR through LLR measurements.

Overall, this study suggests that various MOCR metrics can be derived differently in distinct parts of the auditory system, providing a wide range of perspectives on the influence of MOCR on different auditory structures, mechanisms, and behavior.

Limitations

The current study does have several issues that limit our understanding of the efferent effects and their relationship to one another. As noted, one issue pertains to the uniformity of stimuli. Despite selecting 1-kHz for all tests, the level of the 1 kHz tone varied across different measures. For instance, LLR employed a 60 dB SPL, OAE used 75 dB SPL, and the tone-detection test employed a tone of varying intensity (depending on the subject's threshold). Although the target frequency remained consistent across these studies, the use of different stimuli in the examinations may introduce limitations when measuring the MOCR effect. This is especially true if the MOCR effect is not the same at all sound levels. Specifically, when employing higher levels of noise, the magnitude of the MOC effect becomes more pronounced, and this intensity varies among individuals. To tackle this issue, you can choose to utilize a single tone level or activate a solitary MOCR activator. This strategy aims to boost reliability by minimizing discrepancies between studies as much as possible.

Another limitation is the duration of the study. Completing all three studies (OAE, LLR, Tone-detection) requires approximately 4 hours. Despite providing sufficient rest time based on the participant's condition, engaging in three tasks consecutively can lead to participant fatigue. Holtmann et al. (2023) argued that as the study time increases, the effects of MOCR become less apparent. In the current study, OAE took approximately 5 minutes during the initial performance, tone-detection required 40 minutes, and LLR took approximately 2 hours. Specifically, during the LLR measurement, a higher frequency of artifacts was observed in the final measurement compared to the initial measurement in this study. This heightened fatigue results in an increase in eye blinking and movement, both of which contribute to a higher occurrence of artifacts and necessitate additional time for the measurements. Nevertheless, it is important to acknowledge that measuring the MOCR effect based on SNR, as outlined in aim 2, requires a considerable amount of time. Therefore, it is crucial for future studies to consider these factors and ensure participants receive sufficient rest during Visit 2. This is due to the observed increase in artifact as the subject experiences fatigue and more eye blinking over time. Another issue is the quality of data, specifically, for the 5 dB SNR condition using 55 dB ipsilateral noise. For this condition, subjects tended to exhibit a higher number of artifacts and poorer morphology responses. To address this issue, the number of measurements was increased from 4 to 5 trials in previous assessments. However, despite these efforts, it yielded a poor morphology result compared to measurements conducted using other types

of noises. Consequently, measuring the MOCR effect at low SNR can be somewhat limiting in terms of obtaining reliable results.

Future Work

One suggestion I can make is to standardize the tone-sound level across studies. The varying tone levels used in each study, as highlighted as a limitation in the current research, may impede the understanding of this association between pre-neural response and neural response, and behavioral response in response to MOCR-mediated unmasking. Additionally, although the current study employed a 1 kHz tone to consider the density of the MOC, no significant correlation was found between different MOCR metrics during the study. Therefore, an effective approach to studying the effect of the auditory efferent system could be to measure the overall MOCR strength using clicks. Alternatively, measuring the MOCR effect using chirps is also a viable option. Smith et al. (2017) reported greater MOC responses when using chirps compared to clicks.

Currently, all studies were conducted within a single visit. As mentioned earlier, the duration required for these studies was approximately 4 hours, and in some cases, it took nearly 5 hours depending on the individual. Conducting research over such extended periods has resulted in several limitations, such as an increase in artifacts or a decrease in the MOCR effect. Therefore, reducing the study's interference by conducting more than two visits can be beneficial.

Thirdly, the currently utilized CAEP measures the late response of the auditory efferent system. Thus, by measuring the MOC effect in the early and middle neural responses, it would enable us to comprehend the sequence of changes influenced by MOCR.

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