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Role of The Cochlea and Efferent System in Children with Auditory Processing Disorder

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A thesis submitted in partial fulfillment of the requirements for the degree in Doctor of Philosophy

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by

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Abstract

Auditory processing disorder (APD) is characterized by difficulty listening in noisy environments despite normal hearing thresholds. APD was previously thought to be restricted to deficits in the central auditory system. The current work sought to investigate brainstem and peripheral mechanisms that may contribute to difficulties in speech understanding in noise in children with suspected APD (sAPD). Three mechanisms in particular were investigated: cochlear tuning, efferent function, and spatial hearing.

Cochlear tuning was measured using stimulus frequency otoacoustic emission (SFOAE) group delay. Results indicate that children suspected with APD have atypically sharp cochlear tuning, and reduced medial olivocochlear (MOC) functioning. Sharper-than-typical cochlear tuning may lead to increased forward masking. On the contrary, binaural efferent function probed with a forward masked click evoked OAE (CEOAE) paradigm indicated that MOC function was not different in typically developing (TD) children and children suspected with APD. A third study with multiple OAE types sought to address this contradiction. Despite numerically smaller MOC inhibition in the sAPD group, MOC function was not significantly different between the two groups. Finally, spatial release from masking, localization-in-noise and interaural time difference thresholds were compared in TD and children with sAPD. Results indicate no significant difference in spatial hearing abilities between the two groups. Non-significant findings at group level in these studies may be related to the large heterogeneity in problems associated with APD. Fragmentation of APD into deficit specific disorders may facilitate research in identification of the specific anatomical underpinnings to listening problems in APD.

Prior to conducting studies in children, three studies were conducted to optimize stimulus characteristics. Results of these studies indicate that the MOC may not be especially sensitive to 100 Hz amplitude modulation, as previously reported.

Click stimulus presentation rates >25 Hz activate the ipsilateral MOC reflex in typical MOC assays, contaminating contralateral MOC inhibition of CEOAEs. Finally, localization-in-noise abilities of TD children are on par with adults for a white noise masker, but not for speech-babble. This finding suggests that despite maturation of physiological mechanisms required to localize in noise, non-auditory factors may restrict the ability of children in processing complex signals.

Keywords

Auditory processing disorder, otoacoustic emission, medial olivocochlear, cochlear tuning, localization, spatial hearing, spatial release from masking, interaural time difference, amplitude modulation, click rate

List of Abbreviations

A		
	AAA	American Academy of Audiology
	AM	Amplitude Modulation
	ANSI	American National Standards Institute
	APD	Auditory Processing Disorder
	ASHA	American Speech-Language and Hearing Association
B		
	BBN	Broadband Noise (uniform and random)
	BIC	Binaural Interaction Component
	BSA	British Society of Audiology
C		
	CEOAE	Click Evoked Otoacoustic Emission
	CISG	Canadian Interorganizational Steering Group for Speech-Language Pathology and Audiology
	CI	Confidence Interval
D		
	dB	Decibel
	DPOAE	Distortion Product Otoacoustic Emission
F		
	FBpc	Front-Back Percent Correct responses
	FDR	False Discovery Rate
H		
	HINT	Hearing In Noise Test
	HL	Hearing Level
I		
	ITD	Interaural Time Difference

L

LiSN	Listening in Spatialized Noise
Lscat	Lateral Scatter of responses
LSFA	Least Square Fit Algorithm

M

MEMR	Middle Ear Muscle Reflex
MOC	Medial Olivocochlear system

P

peSPL	Peak Equivalent Sound Pressure Level

O

OAE	Otoacoustic Emission
OHC	Outer Hair Cell

R

RM-ANOVA	Repeated Measures Analysis of Variance
RMS	Root Mean Square
RTS	Reception Threshold for Sentences

S

sAPD	Suspected APD
SB	Speech Babble
SD	Standard Deviation
SFOAE	Stimulus Frequency Otoacoustic Emission
SL	Sensation Level
SNR	Signal-to-Noise Ratio
SPL	Sound Pressure Level
SRM	Spatial Release from Masking
SSW	Staggered Spondaic Word test

T

TBOAE	Tone Burst evoked Otoacoustic Emission
TD	Typically Developing

Co-Authorship Statement

This thesis includes nine chapters: an introductory chapter providing background information and rationale for the work (Chapter 1), seven integrated manuscripts (Chapters 2 through 8), and a concluding chapter (Chapter 9). I, Sriram Boothalingam, am responsible for the conception and design of this work, project coordination, data collection and organization, statistical analyses, and interpretation of results. I am the lead author on all manuscripts included in this thesis, and am the sole author of the introductory (Chapter 1) and conclusion chapters (Chapter 9). The introductory chapter was reviewed by Dr. David Purcell, Dr. Susan Scollie and Dr. Chris Allan prior to inclusion in this document. The conclusion chapter was reviewed by Dr. David Purcell, Dr. Susan Scollie, Dr. Prudence Allen, and Dr. Chris Allan prior to inclusion in this document. Chapter 2 was co-authored by Dr. David Purcell and Dr. Susan Scollie and is published (Boothalingam, S., Purcell, D. W. and Scollie, S., 2014). Dr. David Purcell provided guidance on methods and analyses, and Dr. Susan Scollie provided guidance in statistical analyses. Both co-authors reviewed the chapter prior to inclusion. Chapter 3 was co-authored by Dr. David Purcell who provided guidance on methods and analyses, and reviewed the chapter prior to inclusion. Chapters 4 and 8 were co-authored by Dr. Ewan Macpherson, Dr. David Purcell, Dr. Chris Allan and Dr. Prudence Allen. Dr. Ewan Macpherson and Dr. David Purcell provided guidance on study methods, design and analyses, Dr. Prudence Allen reviewed study methods and provided valuable inputs. Dr. Chris Allan assisted in data collection. Dr. David Purcell, Dr. Ewan Macpherson, and Dr. Chris Allan reviewed chapters prior to inclusion. Chapters 5 and 7 were co-authored by Dr. David Purcell, Dr. Chris Allan, and Dr. Prudence Allen. Dr. David Purcell provided guidance on methods and analyses, and reviewed the chapters, Dr. Prudence Allen provided valuable inputs on study designs and reviewed chapter 5. Dr. Chris Allan assisted with data collection and reviewed the chapters prior to inclusion. Chapter 7

was co-authored by Anders Christensen, Dr. Chris Allan, Dr. Prudence Allen, and Dr. David Purcell. Anders Christensen developed a program to record and analyze distortion product otoacoustic emission that was used in this study, he also provided technical support. Dr. Prudence Allen provided inputs on study methods, Dr. Chris Allan assisted with data collection and reviewed the chapter. Dr. David Purcell provided guidance on study methods, design and analyses, and reviewed the chapter prior to inclusion in the thesis.

Dedication

I dedicate this work to my parents and parents-in-law

for their love, support and faith

and to Viji Easwar,

who laughs for my silly jokes, and has put up with me patiently for the last nine years.

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This thesis is a product of four years of hard work of many individuals to whom I am sincerely grateful.

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My time at the NCA was further made enjoyable by my past and present lab mates; I am grateful for their company and support.

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Contents

List of Figures

List of Tables

List of Appendices

Chapter 1

Contributions of Auditory Noise Reduction Mechanisms in Auditory Processing Disorder

1.1 The Noisy World

The environment that we live in is acoustically dynamic, in the sense that time varying and overlapping sounds are omnipresent. Some sounds are essential for promoting communication and for perception of space, but some are undesirable. These undesirable sounds are typically called noise (Knecht, Nelson, Whitelaw, & Feth, 2002). Noise competes with relevant signals as a result of peripheral masking in the cochlea, and central masking that competes for cognitive resources even in the absence of any peripheral masking. The former phenomenon is called 'energetic masking', while the latter is 'informational masking'[1]. In both cases the result is reduced speech perception. On an evolutionary scale, detection of signals amidst a noisy background would be beneficial in locating a food source and avoiding predators (Endler, 1992). In today's world, listening to relevant signals such as speech is critical for communication and language development in children.

[1]Informational masking is a term used to describe elevation of thresholds that cannot be explained by energetic masking caused by overlapping of signal and masker frequency on the basilar membrane, causing reduction in signal representation in the neural system (Lutfi, Kistler, Oh, Wightman, & Callahan, 2003).

Optimal noise levels have been recommended for classrooms to facilitate speech perception and learning, considering a typical child would spend most of his/her formal learning time in school (American National Standards Institute [ANSI], 2010; American Speech-Language-Hearing Association [ASHA], 2005a). ASHA (2005a) recommended that noise levels in an unoccupied classroom must be no more than 35 dBA SPL. However, studies have shown that noise levels in classrooms range from 28-71 dBA SPL (Crukley, Scollie, & Parsa, 2011; Knecht et al., 2002). For speech to be understood clearly at a comfortable level, its level must be sufficiently higher than background noise. The ratio of the two is typically expressed as signal-to-noise ratio (SNR). Bradley and Sato (2008) reported that younger children (6 years) required an SNR of 15.5 dB to obtain 95% speech intelligibility, while older children (11 years) required a lower SNR of 8.5 dB. Using a sentence perception task, Soli and Sullivan (1997) showed that six year olds required SNR of -1 dB to perform at 50% correct levels, while adults could achieve similar performance at -4 dB SNR.

It is clear that children require a higher SNR than adults to understand speech clearly. Although ASHA (2005a) has recommended a minimum SNR of +15 dB for classrooms, Bradley and Sato (2008) suggested that +15 dB SNR is inadequate for six year olds. A more critical issue is that classroom SNRs can be as low as -7 dB (Crandell & Smaldino, 2000). Children expend considerable listening effort to understand speech at such low SNRs. Howard, Munro, and Plack (2010) reported that children's performance on dual tasks was significantly reduced in the presence of classroom level noise. A common dual task in typical classrooms would be listening to the teacher and writing notes simultaneously. If a child expends a considerable amount of mental effort merely to listen to the teacher, he/she may not be able to take notes efficiently or more importantly, synthesize what is being spoken. This may disrupt the learning process. Indeed, studies show that schools located near airports and highways

have a higher percentage of 'poor readers' (after controlling for socioeconomic status), i.e., children whose reading ability is 1-2 years below their grade level (e.g. Evans & Maxwell, 1997). This situation is further complicated if the child is not a native speaker of the language of instruction (Nilsson, Gelnett, Sullivan, Soli, & Goldberg, 1992).

Poor auditory processing skills have been linked to several developmental disorders, such as dyslexia (e.g. Ahissar, 2007; Chandrasekaran, Hornickel, Skoe, Nicol, & Kraus, 2009; Ziegler, Pech Georgel, George, & Lorenzi, 2009), reading/learning disability (e.g. Bradlow, Kraus, & Hayes, 2003; Cunningham, Nicol, Zecker, Bradlow, & Kraus, 2001; Hornickel, Skoe, Nicol, Zecker, & Kraus, 2009), specific language impairment (e.g. Ferguson, Hall, Riley, & Moore, 2011), and auditory processing disorder (APD; Chermak, Tucker, & Seikel, 2002). For instance, the 'anchoring' deficit hypothesis posits that children with dyslexia are unable to exploit the predictability of repeating acoustic events to enhance SNR (Ahissar, 2007), a phenomenon related to auditory stream segregation (Bregman, 1993). But how are most children able to perform well in school despite such unfavorable acoustic conditions?

1.2 Auditory Noise Reduction Mechanisms

The auditory system employs several mechanisms to combat noise, and promote speech perception in adverse listening conditions. The process of segregating noise from speech begins in the cochlea and continues up to the cortex; this is the 'bottom-up' route. There are also reciprocal connections from cortex to cochlea that further aid in noise reduction in the system by selectively amplifying relevant information. All auditory mechanisms and their corresponding processes contribute to speech perception in noise in some way, however, the focus of this thesis will be on three particular

mechanisms:

(a) Cochlear tuning

(b) Efferent System

(c) Spatial hearing

  (c.1) Auditory localization

  (c.2) Spatial release from masking

Reasons for selection of these three processes pertain to the paucity of information on their role in children with APD, the study group in this work. Children with APD are well suited for the study of these mechanisms because their prime complaint is difficulty listening in noise despite normal hearing ability, among other complaints such as difficulty following instructions, prosody, or rapid speech (American Academy of Audiology [AAA], 2010). Naturally, understanding the role of auditory noise reduction mechanisms in these children may provide insights into their atypical behavioral manifestations, and may also help us understand their role in good listeners. Physiology of these noise reduction mechanisms are reviewed first, following which, their implications for APD are discussed.

The basilar membrane in the cochlea decomposes incoming signals into their individual constituent frequencies (Békésy, 1947), a discovery that fetched a *Nobel* prize. Békésy's experiments, however, fell short of explaining the sharp frequency tuning seen in auditory nerve fibers (ANF). His cadaveric cochleae only exhibited broad tuning due to the lack of the vulnerable cochlear active process. It is now well understood that the sharp tuning within the cochlea is critical for 'normal' hearing, and frequency selectivity in the auditory system, especially in noise (Dorman, Loizou,

Fitzke, & Tu, 1998; Shera, Guinan, & Oxenham, 2002). Along the ascending auditory pathway, the next major processing centre is the superior olivary complex (SOC) where binaural interaction of inputs from individual cochleae takes place. Binaural interaction is fundamental to auditory processes such a sound localization and spatial release from masking (SRM; Grothe, Pecka, & McAlpine, 2010).

Localization aids in formation of auditory streams which the brain uses to segregate wanted from unwanted sounds based on their location (Bregman, 1993). Speech perception in noise is further facilitated with the aid of working memory, and cognitive processes such as attention at higher auditory (and related) centers in the cortex (Colflesh & Conway, 2007; Salamé & Baddeley, 1987). Also, the cortex fine-tunes bottom-up signals by selectively enhancing relevant information while inhibiting others via its vast efferent network (Luo, Wang, Kashani, & Yan, 2008; Perrot et al., 2006; Winer, 2006). Attention is known to play a large role in this fine tuning process, both at the cortical level (Kauramäki, Jääskeläinen, & Sams, 2007; Okamoto, Stracke, Wolters, Schmael, & Pantev, 2007), and at the periphery (de Boer & Thornton, 2007; Maison, Micheyl, & Collet, 2001). The efferent auditory pathway ends in the cochlea with axons of the medial olivocochlear system (MOC) contacting outer haircells (OHCs; Warr & Guinan, 1979).

1.2.1 The Cochlea and Cochlear Tuning

The cochlea is a low noise, energy efficient, and adaptive amplification device that surpasses any human-made digital or analog amplification system. It works as a frequency analyzer by transforming frequency information into spatial positions along the basilar membrane. This remarkable feat is made possible by the apically propagating traveling wave, and dictated by the stiffness gradient of the basilar membrane (Pickles, 2008). The traveling wave progressively slows down, and peaks at its char-

acteristic frequency (CF) before perishing. The peak occurs at the CF because this is where the impedances of the mass and elasticity of the basilar membrane cancel out to cause resonance for a given frequency. As remarkable as it is, this process only produces a broad and off-CF centered peak activation of outer hair cells (Yates, 1995). So, how is the tuning of auditory nerve fibers that innervate the inner hair cells much sharper?

The impressive tuning and dynamic range (120 dB) observed in the auditory system is accomplished with the help of the "cochlear amplifier". The cochlear amplification process is essentially the electromotile OHCs feeding energy back into the traveling wave, amplifying their transverse motion for low level sounds close to the CF on a cycle-by-cycle basis (Kemp, 2007). Two prevailing theories explain the mechanisms behind the active amplification process: OHC electromotility (Brownell, Bader, Bertrand, & de Ribaupierre, 1985), and OHC hair-bundle motility (Martin & Hudspeth, 1999). OHC electromotility is the ability of the OHCs to undergo rapid voltage-dependent mechanical changes in length (contraction - when depolarized and expansion - when hyperpolarized), and stiffness, owing to the motor protein *prestin* (Zheng et al., 2000). These length changes are thought to boost the basilar membrane traveling wave just basal to the CF of the evoking stimulus. OHC hair-bundles have also been reported to produce active movements that feed-back into the basilar membrane in the direction of the force applied. Neither of these proposed mechanisms completely explain the amplification process, but the hair-bundle motility draws much criticism (Pickles, 2008). Mathematical modeling efforts show that OHC electromotility is necessary for the cochlear active process while hair-bundle motility is not. However, Ramamoorthy, Deo, and Grosh (2007) reported that inclusion of hair-bundle motility in their model explained experimental results of basilar membrane motion better than OHC motility alone. Therefore, they suggested that

both these mechanisms should work in a synergistic manner.

Whatever may be the underlying mechanism, cochlear amplification is pivotal for 'normal' hearing and sharp frequency tuning in the auditory system. Without cochlear amplification our hearing thresholds would be 40-60 dB worse (Liberman et al., 2002), and frequency selectivity at the traveling wave peak, i.e., cochlear filtering, would be 20-60 dB broader (Robles & Ruggero, 2001). Sharpness of the cochlear filter, i.e., tuning, is also important for resolving harmonics and pitch perception (Oxenham, Bernstein, & Penagos, 2004). Recent studies have shown that human cochlear tuning is three times as sharp as other animals (guinea pigs, cats et cetra), an evolutionary advantage that is thought to aid in processing of speech signals (Shera et al., 2002; Shofner, 2014). Loss of cochlear amplification, as occurs in cochlear hearing loss, leads to reduced audibility and widened auditory filters, affecting frequency resolution (B. C. J. Moore, 2003). While amplification devices can be used to restore audibility, loss of sharp cochlear tuning cannot be compensated by any means (Peters, Moore, & Baer, 1997). Broad tuning of cochlear filters is one of the prime causes of speech-in-noise difficulties in individuals with hearing loss. This is due to the filter becoming particularly vulnerable to the masking effects of noise, either due to upward or downward spread of masking, depending on the affected frequency skirt of the filter (Glasberg & Moore, 1986; B. C. J. Moore, 1991).

Typically, broader tuning, or poor frequency selectivity, is only associated with cochlear hearing loss (B. C. J. Moore, 2003). However, Patterson, Nimmo-Smith, Weber, and Milroy (1982) first showed that auditory filter widths increased, i.e., tuning deteriorated, as a function of age from 23-72 years in individuals with clinically normal audiograms. They also reported that reduced speech intelligibility appeared to closely relate to the reduction of frequency selectivity in the cochlea. More re-

cently, Badri, Siegel, and Wright (2011) investigated cochlear tuning in individuals with speech perception difficulties in noise but with clinically normal audiograms. Their findings were similar to that of Patterson et al. (1982); individuals with speech perception difficulties had broader cochlear tuning. Interestingly, these individuals also had elevated hearing thresholds at high frequencies (>8 kHz). Results of these studies suggest that clinical audiograms are not sufficient to uncover underlying problems in some individuals with speech in noise difficulties. These findings may have implications for children with APD, whose hallmark is difficulty listening in noise despite clinically normal audiograms (Chermak et al., 2002). Considering noise in classrooms are low-mid frequency in nature (Crukley et al., 2011), increased upward spread of masking may pose considerable speech perception difficulties in children who have broader cochlear tuning.

Despite the benefits of sharp cochlear tuning, the time-frequency trade-off in filter responses cannot be overlooked. Considering that the basilar membrane acts like a filter, filter theory dictates that sharp frequency tuning would come at the expense of longer filter ringing [(Oppenhiem and Wilsky (1997) cited in: Francis & Guinan, 2010)]. Zheng et al. (2011) indicated that an exceptionally sharp filter will cause longer lasting basilar membrane vibrations, and may forward mask an incoming signal's response. Longer filter ringing can thus potentially reduce temporal resolution in the auditory system. Indeed, Shailer and Moore (1983) showed that gap detection[2] is poorer at lower frequencies owing to longer ringing times of the relatively sharper low frequency basilar membrane filters. Therefore, optimal cochlear tuning may be better suited for speech-in-noise perception than an exceptionally sharp filter. Cochlear tuning is mature at full-term birth (Abdala, 2001; Abdala & Chatterjee, 2003), and can be tested objectively using otoacoustic emissions (OAEs). Therefore, further

[2]As an assay to measure temporal resolution, the gap detection task measures listeners' ability to identify the smallest temporal gap between a pair of stimuli.

investigation of tuning using OAEs in individuals with speech-in-noise difficulties may help delineate subtle underlying irregularities.

1.2.2 The Efferent System

The efferent system begins in the cerebral cortex, and forms a corticofugal network that contacts several auditory nuclei as it traverses towards the periphery. Independent corticothalamic, corticocollicular, and corticobulbar tracts have been identified (review: Winer, 2006). These networks have been posited to fine-tune bottom-up signal encoding, and control gain in the system such that salient information can be extracted easily (Robinson & McAlpine, 2009; Schofield, 2010). The topic of interest here is the final leg in this efferent projection: the superior olivary complex's (SOC) olivocochlear bundle (OCB). This is because, the OCB contacts cochlear outer haircells directly, and the type-I afferent fibers just beneath the inner haircells, thereby exerting a fine-tuning process right at the auditory periphery. In turn, cortico-olivary projections contact the OCB directly (Coomes & Schofield, 2004; Mulders & Robertson, 2000), or through indirect connections that traverse via various collicular nuclei, and modulate their reflexive activity (Huffman & Henson, 1990).

Based on cell types and myelination of axons, two separate systems in the OCB have been identified: the lateral olivocochlear reflex (LOC) and the medial olivocochlear reflex (MOC; Warr & Guinan, 1979). Considering the LOCs are unmyelinated, almost all efferent effects in the cochlea are attributed to the MOC (Guinan, 2010). Indeed, little is known about the LOC; therefore, this thesis will focus only on the role of MOC as a noise reduction mechanism.

The Medial Olivocochler Reflex

MOC neurons can be grouped as ipsilateral and contralateral units; the former respond to monaural sound in the ipsilateral ear, and the latter to the contralateral ear. There are also neurons that respond to binaural and either-ear stimulation (Liberman & Brown, 1986), although the majority of MOC neurons respond to binaural stimulation (Brown, Kujawa, & Duca, 1998). In humans, MOC neurons are found scattered around the medial superior olive (MSO) in a manner that separate nuclei cannot be defined (J. K. Moore, 1987). MOC neurons receive ascending inputs from the ventral cochlear nucleus, evident from their short latency (Ye, Machado, & Kim, 2000). A single MOC axon can receive multiple frequency inputs from the ventral cochlear nucleus, making them particularly sensitive to noise (Liberman, 1988). They also receive descending inputs from the inferior colliculus (Mulders & Robertson, 2000), and direct inputs from the cortex (León, Elgueda, Silva, Hamame, & Delano, 2012).

MOC axons directly innervate the OHCs tonotopically, albeit with asymmetric density across frequencies (Guinan, 2006). Recent studies show that the functional frequency specificity of MOC innervation in the cochlea is rather poor (Lilaonitkul & Guinan, 2012; Zhao & Dhar, 2012). Stimulation of the MOC, causes the inhibitory neurotransmitter acetylcholine to inhibit the putative cochlear active process (Guinan, 2006). Acetylcholine causes calcium gated potassium channels in the OHC to open, which reduces its basolateral resistance. The basolateral resistance permits the essential voltage drop across the OHC, and is required for driving the cochlear amplifier. A drop in OHC resistance drains charge from the scala media causing a drop in OHC direct current (DC) voltage. Therefore, the voltage drive to the motor protein, *prestin*, is reduced. Thus, MOC activity essentially hyper-polarizes the OHC and reduces cochlear amplification, which is reflected as reduced neural output and OAE amplitude (Robertson, 2009).

The prevalent model that explains implications of MOC inhibition of OHC activity is the "unmasking model" (Guinan, 2006). This model argues that noise overdrives OHC activity and saturates the ANF responses, reducing the dynamic range of ANF as a result. Reduced dynamic range would not allow for coding of novel incoming time-varying stimuli such as speech. Inhibition of OHC activity by the MOC is thought to restore some of the lost dynamic range, allowing for incoming stimuli such as speech to be coded on to ANF (Kawase, Delgutte, & Liberman, 1993; Winslow & Sachs, 1988). Thereby, the MOC unmasks time-varying signals whose neural representation in the auditory system would otherwise be masked by noise. MOC unmasking has been correlated with concurrent improvements in behavioral measures of speech perception in noise (de Boer, Thornton, & Krumbholz, 2012; Giraud et al., 1997; Kumar & Vanaja, 2004; Mishra & Lutman, 2014). MOC function also explains variability in localization-in-noise (Andéol et al., 2011), protection against acoustic trauma (Rajan, 2000), and is responsible for proper development of the auditory system itself (Pujol, Carlier, & Devigne, 1979). It can thus be envisaged that reduced MOC function may increase vulnerability to peripheral masking, and reduce SNR in the system. In addition, atypical MOC function may also point towards potential developmental cochlear irregularities (Abdala, 2001).

1.2.3 Spatial Hearing

Spatial hearing is the ability of the auditory system to use binaural cues to form a perceived representation of space, and aid speech perception in noise. Both these properties aid higher level processes such as stream segregation in further improving SNR in the system (Culling & Akeroyd, 2010). Naturally, the precursor to spatial hearing is binaural hearing, i.e., listening through two ears. In addition to spatial processing, there are several advantages to listening binaurally. When the same sig-

nal is processed through two ears, an improvement in hearing occurs (1-2 dB SNR, 3 dB improvement in thresholds) due to redundancy of information in the system (MacKeith & Coles, 1971). Other advantages include: improvement in frequency selectivity and intensity discrimination (Jesteadt & Wier, 1977), ease of listening (Feuerstein, 1992), and improved speech perception (Helfer, 1994). But specifically, how does spatial hearing help in noise reduction?

Auditory Localization and Spatial Release from Masking

The auditory system uses two one-dimensional cues (azimuth and elevation) to map the three dimensional space around us. This remarkable feat is achieved with the help of several cues working in tandem. For sounds occurring in the horizontal (azimuthal) plane, the auditory system uses timing and level differences between signals arriving at the two ears. These cues are aptly named, interaural time difference (ITD) and interaural level difference (ILD), respectively (Culling & Akeroyd, 2010). Wavelength (therefore frequency) of a signal dictates which cue is used for horizontal plane localization. For example, when sounds are presented from the right, low frequency sounds reach the left ear with a time delay relative to the right ear (i.e. ITD), but without much loss of energy, due to their large wavelengths. For high frequency sounds, the head casts a shadow for the left ear due to their shorter wavelengths, effectively reducing the signal level, and thus creating an ILD (review: Middlebrooks & Green, 1991). However, both ITD and ILD do not provide differential information for sounds occurring in the median plane, i.e, front/back and up/down. This is because a sound in the median plane would reach both ears at the same time and at the same level. Instead, the auditory system uses spectral differences engendered by pinna, head and torso to resolve front/back and up/down confusions (Wightman & Kistler, 1989).

Effective noise reduction in the auditory system is achieved by spatially separating

masker and speech, which provides a relative improvement in speech perception. This phenomenon is called spatial release from masking (SRM; Freyman, Helfer, McCall, & Clifton, 1999; Hawley, Litovsky, & Colburn, 1999; MacKeith & Coles, 1971). The more complex the acoustic environment, the larger the SRM (Johnstone & Litovsky, 2006). This suggests that the auditory system relies more on spatial hearing in adverse listening conditions. There are several mechanisms by which the auditory system achieves SRM (Arbogast, Mason, & Kidd, 2002; Bregman, 1993; Litovsky, 2012);

(a) Better ear listening: essentially ILD

(b) Binaural unmasking: essentially ITD

(c) Binaural squelch: utilizes both ITD and ILD to suppress noise in the system

(d) Binaural summation: summation of signals from both ears, improves overall SNR

(e) Localization: facilitates stream segregation

When masker and noise are in separate hemi-fields (e.g. left and right), at least one ear would receive a better SNR, and this apparent ILD improves speech perception. This phenomenon is thought to explain the bulk of SRM in a "cocktail party" situation, but does not provide benefit when masker and speech occur in the same hemi-field (Culling, Hawley, & Litovsky, 2004; Litovsky, 2012). Binaural unmasking on the other hand, uses the auditory system's ability to read ITD to separate noise and speech, therefore it is robust even when noise and speech occur in same hemi-field (Culling et al., 2004). A typical example of binaural unmasking is the binaural masking level difference (BMLD), where a phase difference in either the masker or signal causes an improvement in signal thresholds. Binaural squelch is the term given to central auditory processing that utilizes both ILD and ITD in adverse listening conditions to parse speech and noise (MacKeith & Coles, 1971). Binaural summation causes an improvement in SNR, simply because the same stimulus (typically from the

front) is added with itself in the auditory system due to binaural inputs, causing an increase in signal representation (MacKeith & Coles, 1971). Finally, localization of the target source improves speech perception in a noisy environment by directing attention to the relevant source signal. This is analogous to turning one's gaze towards a desired visual source. The auditory system would then be able to parse relevant information based on direction, i.e., by grouping acoustic events from one direction into a single related event (Bregman, 1993).

Localization is thought to contribute less to stream segregation when compared to other means such as tracking the pitch of a talker (Bregman, 1993). It has also been shown to be trivial for improving speech perception compared to better ear listening and binaural unmasking (Culling et al., 2004; Hawley, Litovsky, & Culling, 2004). Some researchers do suggest that perceptual spatial separation, i.e., knowledge of location of the target/masker aids significantly in masking release for informational maskers (Arbogast et al., 2002; Arbogast, Mason, & Kidd, 2005; Freyman et al., 1999; Kidd, Arbogast, Mason, & Gallun, 2005). Arbogast et al. (2002) demonstrated this effect by generating speech stimuli using a cochlear implant simulator. By allotting different modulation frequencies for speech and noise stimuli, they eliminated binaural unmasking, yet they observed SRM. The obtained masking release was much higher (18.6 dB) than what could be explained using better ear listening and binaural unmasking. Therefore, they suggested that SRM in the informational masking condition is more perceptual than acoustic.

Resolving fundamental questions on SRM was not the motive of this thesis, rather the focus was on measuring localization abilities in noise and SRM in children. Even though there is no clear consensus yet on the role of localization in SRM (Culling & Akeroyd, 2010), it is a valuable tool for testing binaural hearing. Considering,

maturation of localization starts early in life and children localize at adult levels at as young as 5 years (Litovsky, 1997; Van Deun et al., 2009), localization and SRM may serve as a test to detect abnormalities in binaural hearing (Hall & Grose, 1993). On the other hand, children's ability to localize in noise is relatively unknown, despite studies showing that children as young as three years show robust SRM (Garadat & Litovsky, 2007). Understanding localization-in-noise in children is crucial because localization itself is not immune to noise. Studies in adults show that localization ability deteriorates before the signal becomes inaudible (Good & Gilkey, 1996). It is unclear how well children are able to localize in noise, especially children with APD.

1.2.4 Implications of Auditory Noise Reduction Mechanisms

The aforementioned noise reduction mechanisms work in tandem to improve both signal integrity (at the cochlea), and response fidelity (in neural systems) in the auditory system. In addition, the auditory system has high 'intrinsic' redundancy, making it less vulnerable to the effects of noise and pathologies (Krishnamurti, 2007). However, breakdown in any of these processes can lead to subtle deficits in signal processing, or reduce an individual's ability to take advantage of available cues to, at the least, reduce mental effort in listening (Howard et al., 2010). Evidence from older normal hearing and presbyacusic adults shows that reduction in working memory capacity, either due to age or noise, can lead to reduced speech perception in noise (Pichora-Fuller, Schneider, & Daneman, 1995). Conversely, it can be thought that 'freeing-up' these mental resources can aid speech perception in noise.

A conceptual model, shown in Figure 1-1 was created to hypothesize and visualize possible outcomes of the three noise reduction mechanisms, and their interconnections, that may impact speech perception in noise. Briefly, broad cochlear tuning can increase masking effects, and thus reduce speech perception in noise. On

the contrary, exceptionally sharp tuning can cause forward masking effects, reducing temporal resolution in the system, which may also lead to reduced speech perception. Reduced MOC function can reduce SNR in the system, and may cause difficulties in speech perception in noise.

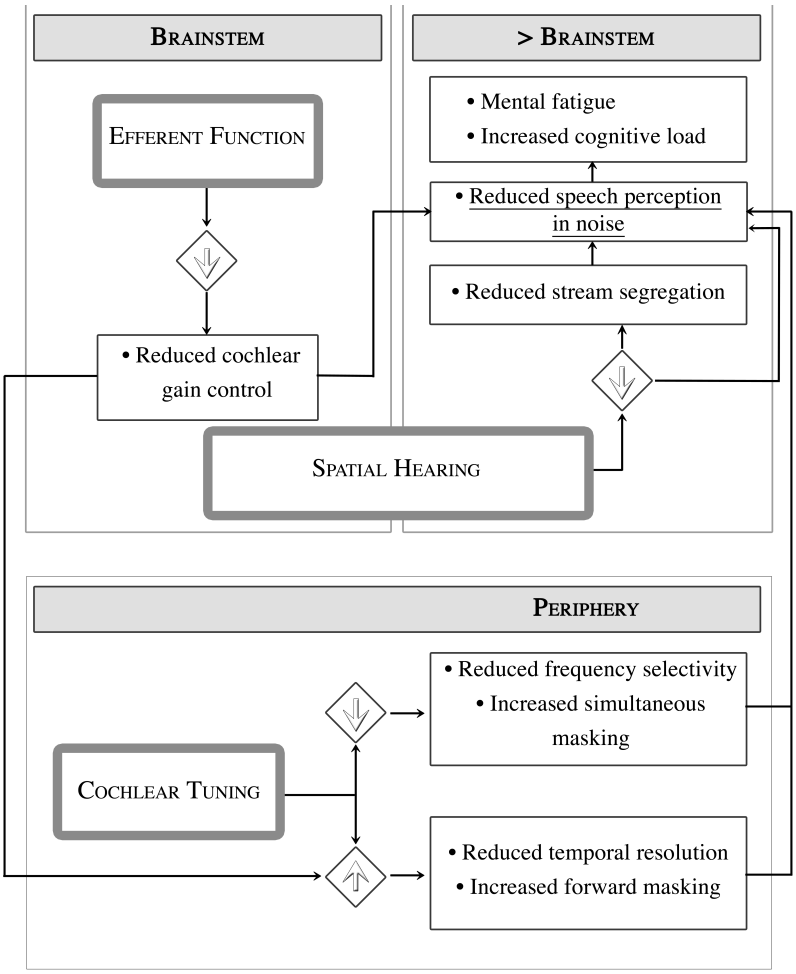

Figure 1-1: A conceptual model involving the three noise reduction mechanisms, placed under their respective anatomical positions. Filled thin black arrows connect processes/mechanisms to their further consequential outcomes. Unfilled grey arrows inside decision boxes indicate sharp (up arrow) or broad (down arrow) tuning, reduced MOC function (down arrow), and reduced localization-in-noise (down arrow). Note that only the processes/mechanisms within thick grey boxes were investigated in this work. Their outcomes are inferred based on empirical evidence from previous studies.

Reduced MOC function can also be related to sharpened cochlear tuning, as reduction in gain control from the MOC may lead to increased cochlear amplification, resulting in exceptionally sharp cochlear tuning (Abdala & Chatterjee, 2003; Abdala, Sininger, Ekelid, & Zeng, 1996). Finally, reduced ability to use spatial cues to separate noise and speech, either energetically (SRM), or perceptually (stream segregation due to localization) may also reduce an individual's speech perception ability in noise. Difficulty in speech understanding in noise will require increased mental effort, and additional working memory resources which may hinder learning in classrooms.

Considering adults and children who do not have speech-in-noise difficulties benefit from these mechanisms, it may be useful to investigate these processes in children who have difficulty in noisy situations. Therefore, the focus of this thesis was investigation of the role of these auditory noise reduction mechanisms in children with APD. Note that only the processes within thick grey boxes in Figure 1-1 were investigated in this work. Outcomes of these processes, and their influence on speech-perception, and ultimately mental effort (e.g., Wild et al., 2012), were inferred from empirical evidence reported in previous studies. Therefore, a direct causal relationship cannot be drawn between these processes and their implications for speech perception in noise. But first, what is APD?

1.3 Auditory Processing Disorder

"A riddle wrapped in a mystery inside an enigma"

- Stuart Rosen, 2005

In the words of Sir Winston Churchill, Rosen (2005) described APD in this way, largely because, despite decades of research, APD remains a topic of immense debate. APD is a highly heterogeneous disorder, involving a breakdown of various aspects of

auditory processing that result in complaints and symptoms that vary considerably across populations (D. R. Moore, 2006). AAA (2010) defined APD as "difficulties in perceptual processing of auditory information in the central nervous system and the neurobiological activity that underlies the processing". APD affects about 2-3% of school age children (Chermak, Somers, & Seikel, 1998). APD may also co-occur with other developmental disorders such as attention deficit hyperactivity disorder (Chermak et al., 1998), dyslexia (Mody, Studdert-Kennedy, & Brady, 1997; Tallal, 1980), specific language impairment (Tallal & Piercy, 1973) and learning disability (Kraus & Zecker, 1996). Sharma, Purdy, and Kelly (2009) reported that language impairment and reading disability commonly co-occurred with APD.

In congruence with the heterogeneity of its symptoms and causes, there is no single test or measure that can diagnose a person as having APD, nor is there any gold standard (Bellis, 2003). Therefore, in clinical assessment a test battery approach is followed based on recommendations from professional Audiology bodies. As recommended by the American Speech-Language-Hearing Association [ASHA] (2005b), and emphasized by the Canadian Interorganizational Steering Group for Speech-Language Pathology and Audiology [CISG] (2012), an APD test battery must include tests that are capable of evaluating several auditory processes, such as, temporal processing, binaural integration/interaction, pattern recognition, speech recognition in competing and degraded acoustic signals, auditory discrimination, and localization. Typically, a child would fail at least two out of five tests to be diagnosed as APD (ASHA, 2005b). However, no recommendations on specific tests are made, therefore, a clinician is free to choose tests of his/her choice. This leads to a considerable mismatch in results across research studies, often rendering them difficult to compare (Allen & Allan, 2014). Behavioral speech-based tests have also been criticized because of their sensitivity to the language ability of the child being tested (Allen & Allan, 2014; British

Society of Audiology [BSA], 2011). For this reason, some researchers argue that primarily non-speech tests must be used to diagnose APD (BSA, 2011; Rosen, 2005).

Although not widely used, objective tests have also been recommended for use as part of the APD diagnosis process (AAA, 2010; ASHA, 2005b). Interest in objective tests is increasing due to two reasons: one, recent studies demonstrate that specific deficits can be identified in various parts of the auditory system (Allen & Allan, 2014; Gopal & Pierel, 1999; Hornickel et al., 2009; Muchnik et al., 2004); two, objective tests eliminate the need for subjective responses that can be influenced by various factors as mentioned above. However, considering there are no guidelines for basing APD diagnosis on objective tests, behavioral tests take precedence in clinical settings (Singer, Hurley, & Preece, 1998). Nevertheless, objective tests are valuable tools for research, especially in unraveling anatomic underpinnings of a behavioral manifestation.

1.3.1 Anatomic Basis of Auditory Processing Disorder

Owing to its heterogeneity involving various perceptual and cognitive manifestations, difficulties reported in APD typically cannot be pinned to a single anatomic place or one impaired process (Banai & Kraus, 2007). Physiological causes of APD, if present, can stem from a neurological lesion anywhere in the auditory system, delayed central nervous system maturation, or other developmental disorders (Bamiou, Musiek, & Luxon, 2001). APD can also result from peripheral hearing loss as occurs in chronic otitis media, leading to deprivation of acoustic input to the auditory system that alters short term plasticity (Hall & Grose, 1993). Therefore, understanding the underlying anatomical basis of APD, as diverse it may be, could help develop objective tests and more focused treatment regimens. For instance, Veuillet, Magnan, Ecalle, Thai-Van, and Collet (2007) identified atypical voice onset time (VOT) sensitivity and reduced

asymmetry[3] in MOC function in children with reading disabilities. Following audio-visual training on a consonant-vowel task that targeted VOT sensitivity, they showed that children's VOT perception improved with a concurrent improvement in MOC functional asymmetry.

Further, objective studies have also highlighted the role of the brainstem in APD (review: Banai & Kraus, 2007), in contrast to behavioral tests, which are typically restricted to testing higher brain centers. APD was indeed previously called central-APD, owing to the notion that only central auditory processing was affected (Jerger & Musiek, 2000). Yet there remain several auditory processes and mechanisms that need to be investigated. Despite the profound implications of cochlear tuning in frequency selectivity in the auditory system, no studies have investigated its role in APD. The peripheral auditory system is merely screened for presence of an overt hearing loss. While previous studies have indicated reduced MOC functioning in children with APD (Muchnik et al., 2004), there is no clear consensus, and studies that show significant group effects suffer from methodological limitations. Finally, position statements and guidelines from professional Audiology bodies such as CISG (2012), AAA (2010) and ASHA (2005b) have indicated that localization is affected in children with APD, although there are no published data. It is unclear if localization is indeed affected in children with APD.

[3]Stronger inhibition of OHC activity by MOC activation in the right ear compared to the left (Khalfa & Collet, 1996)

1.4 Measures to Probe Auditory Noise Reduction Mechanisms in APD

Developing objective measures was not the aim of this thesis, so tools that are already at the disposal of clinicians were predominantly used. This was done in order to allow easier translation of assays to clinical settings, should a biological marker be identified. To this end, assays based on OAEs were central to this thesis. Use of a single measure such as OAEs across studies (except localization) ensured continuity amidst investigations of varied auditory processes and mechanisms.

1.4.1 Otoacoustic emissions

OAEs measured in the ear-canal are extra energy generated as a byproduct of the cycle-by-cycle cochlear amplification process. Considering that OAEs are generated in the cochlea and are measurable in the ear-canal, they serve as a window into the workings of the inner ear (Pickles, 2008). Based on the generation mechanism involved, OAEs can be classified into two types: (1) reflection-type emissions, and (2) distortion-type emissions (Shera & Guinan, 1999). Reflection-type emissions, according to the 'coherent reflection' theory (Zweig & Shera, 1995), are thought to be generated by reflection of the forward traveling stimulus wave due to random impedance perturbations on the basilar membrane at the traveling wave peak. These perturbations could be a difference in force generated by OHCs, their size, their arrangement on the basilar membrane, and the traveling wave itself. This reflection is a linear process mediated by the non-linearity of the cochlear amplifier. Reflected wavelets combine constructively to form a coherent emission (Shera & Abdala, 2012).

With the exception of distortion product OAEs (DPOAEs, e.g. $2f_1 - f_2$), all evoked OAEs are reflection-type emissions, at least at low stimulus levels (Shera &

Guinan, 1999). These include click evoked (CEOAEs), tone-burst evoked (TBOAEs), stimulus frequency (SFOAEs), and spontaneous (SOAEs). Distortion-type emissions are thought to be generated by the non-linear distortion generated due to the overlap of two close-by frequencies stimulating the same OHC. Two wavelets at the overlap region are generated in this process. Wavelets with negative phase that combine constructively on the basilar membrane travel backwards (towards the middle-ear), and reach the ear-canal as acoustic DPOAEs. However, wavelets with positive phase travel towards the $2f_1 - f_2$ place on the basilar membrane. These wavelets essentially are forward traveling waves similar to the pure tones that evoked them. Upon reaching the $2f_1 - f_2$ place on the basilar membrane, the reflection mechanism discussed earlier generates reflection emissions. Therefore, DPOAEs observed in the ear-canal are a composite mixture of both distortion and reflection components. Because the reflection component of the DPOAE is evoked by a much smaller stimulus (re: f_2 level), it is diminutive compared to the distortion component (Kemp, 2007; Shera & Abdala, 2012; Shera & Guinan, 1999).

But what does OAE generation have to do with measuring cochlear tuning and MOC function? Understanding the generation mechanisms of OAEs is critical for their interpretation. For instance, coherent reflection theory predicts, and has been experimentally shown, that the SFOAE group delay is roughly half of basilar membrane group delay for a given frequency (Shera & Guinan, 2003). SFOAE group delay is the total time taken from stimulus presentation to recording a resultant SFOAE in the ear-canal. This includes stimulus travel time from the ear-canal to the CF place on the basilar membrane, building a peak at the CF, generation of backward traveling wavelets of the stimulus frequency that coherently add on the basilar membrane, the reverse travel time on the basilar membrane, and across the middle-ear and ear-canal. However, the traveling wave build-up at the CF accounts for almost the entire time

taken. Middle-ear and cochlear traveling times are negligible (Don, Ponton, Eggermont, & Kwong, 1998; Shera et al., 2002). Therefore, half of this total time-taken (for forward and reverse travel), can be approximated using half of SFOAE group delay, to reflect BM group delay. This is true at least for roughly the basal 60% of the basilar membrane ($\sim$>1 kHz). This relationship can be used to predict cochlear tuning at a given frequency. In addition, filter theory dictates that sharper filters will take longer to build-up (Oppenhiem and Wilsky (1997) cited in: Francis & Guinan, 2010). Therefore, individuals with broad cochlear tuning present with short SFOAE group delays, while individuals with sharper tuning present longer group delays.

Also, OAEs are currently the simplest means to quantify MOC activity on OHCs. This is because, as discussed earlier, MOC innervates the OHCs directly and inhibit the OHC active process, of which the OAEs are a byproduct. Consequently, MOC inhibition of OHC activity also inhibits OAE level and alters its phase, a phenomenon referred to as 'OAE inhibition' (Guinan, 2006). By studying OAE level and phase in separate conditions with and without MOC activation, one can quantify MOC activity, or 'MOC strength' for an individual at a given frequency.

1.5 Purpose of This Thesis

The purpose of this thesis was to investigate the contributions of known auditory noise reduction mechanisms in children with APD in order to understand if a breakdown in any of these mechanisms could explain their listening difficulties in noise. However, we first set out to optimize instrumentation and select stimulus parameters that would ensure success in recording high quality OAEs, as well as behavioral responses in children with APD. This phase was essential because children in general have higher internal noise than adults in any physiological measure, and methods

developed for the purpose of these thesis studies were novel to the employed instrumentation. Chapters 2-4 in this thesis are a result of this optimization phase, where normal hearing adults and children were used as study participants.

Following the optimization phase (Chapters 2-4), four studies were conducted in children with APD. The first study (Chapter-5) investigated cochlear tuning, and its relationship to MOC function. The second study (Chapter-6) investigated binaural MOC function and interaction, and also evaluated group (APD vs. typically developing [TD]) differences in a behavioral correlate of binaural interaction. Contradicting results were obtained between chapters 5 and 6 for MOC function in children with APD. The SFOAE in Chapter-5 indicated reduced MOC strength with APD, but CEOAE in Chapter-6 indicated no such differences between children with APD and TD children. Therefore, the motive of the third study (Chapter-7) was to resolve this conflict by studying MOC function using three different types of OAEs. The aim of the fourth study (Chapter-8) was to investigate localization-in-noise and spatial release from masking abilities in children with APD.

1.6 Chapter Synopses

1.6.1 Instrumentation and Stimulus Optimization Phase

Chapter-2: Influence of 100 Hz Modulation on the MOC

Amplitude modulation (100 Hz) following ability of the MOC was investigated. A previous study had indicated that the MOC is particularly sensitive to 100 Hz modulation (Maison, Micheyl, & Collet, 1999). Considering children with APD have been reported to have reduced MOC functioning, we studied MOC inhibition using a 100 Hz modulated elicitor[4] to possibly enhance MOC activity. A comparison

[4]Elicitor refers to the MOC activating stimulus; typically a broadband noise is used.

of modulation following ability of the MOC between TD, and children with APD was also planned. However, adult data showed that the MOC is insensitive to high modulation rates, and in fact modulations in an elicitor reduced its effectiveness in eliciting MOC activity. Therefore, this stimulus manipulation was not used in further studies.

Chapter-3: Optimal Click Presentation Rate for Recording CEOAEs

In order to interpret observed reduction in OAE level due to MOC activation, several variables need to be carefully controlled. One such variable is the stimulus (click) presentation rate in measuring click evoked OAEs. Faster rates (>50 Hz) have been reported to activate the MOC reflex when presented in the contralateral ear (Veuillet, Collet, & Duclaux, 1991). However, clicks are presented in the ipsilateral ear as the OAE evoking stimulus, in addition to broadband noise elicitors in the contralateral ear. Therefore, it was unclear what click rates would elicit ipsilateral MOC activity in the presence of a contralateral elicitor. A forward masking paradigm was used in this study to investigate this rate effect. It was found that rates as low as 31.25 Hz evoke significant MOC activity.

Chapter-4: Localization-in-noise and MOC Activity in Typically Developing Children and Young Adults

One previous study showed that variability in median plane localization-in-noise ability can be explained partially by MOC strength (Andéol et al., 2011). Considering children with APD have been suggested to have poor localization abilities, and reduced MOC function, we sought to investigate if front/back localization-in-noise in TD children and adults could be explained by MOC strength. Results indicated no correlation between the two variables in both children and adults. Therefore, in Chapter-8, only the localization-in-noise ability of children with APD was investigated, and no attempts were made to correlate localization and MOC strength in

children with APD.

1.6.2 APD Study Phase

Chapter-5: Cochlear Tuning and MOC Function in Children with APD

Cochlear tuning and its relationship to MOC strength was investigated in children with APD. Results showed significantly sharper tuning in children with APD compared to TD children. Children in the APD group also showed an atypical relationship between tuning with MOC strength, as compared to TD children.

Chapter-6: Binaural MOC Function and Interaction in Children with APD

Considering we always listen through both ears, binaural MOC can be expected to be activated in real-life. No previous studies have investigated binaural MOC function in children with APD. Results showed no significant difference in MOC strength, and no difference in binaural MOC interaction between APD and TD groups.

Chapter-7: Is MOC Function Affected in Children with APD?

Conflicting results from Chapters 5 and 6, and from the literature, led to comparison of MOC inhibition of OAEs obtained using three different OAEs (SFOAE, DPOAE, and CEOAE) in this study. Results again were inconclusive.

Chapter-8: Localization-in-noise Abilities of Children with APD

Localization-in-noise in the front/back and lateral domains, spatial release from masking and ITD thresholds were compared between TD and APD groups. Results showed no significant difference between groups, suggesting that not all children with APD have localization difficulties.

Chapter-9: General Discussion, Conclusion and Future Directions

Results of all studies are discussed to arrive at a coherent exposition of this work. Conclusions are drawn based on the present results, strengths and limitations have been identified, and future directions have been proposed.

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Chapter 2

Influence of 100 Hz Amplitude Modulation on the Medial Olivocochlear Reflex[1]

2.1 Introduction

The human auditory system has reciprocal connections through which higher auditory centers influence the working of lower auditory systems; this has been shown in animals models (Winer, 2006; Xiao & Suga, 2002), and humans (Khalfa et al., 2001; Perrot et al., 2006). The final stop in the descending auditory pathway is the medial olivocochlear system (MOC). The MOC hyper-polarizes the cochlear outer hair cells (OHCs) through direct cholinergic action, consequently, reducing the gain of the cochlear active process (Murugasu & Russell, 1996). Reduction in the cochlear active process can be recorded as reduced otoacoustic emission (OAE) level (Guinan, 2006). Such reduction in cochlear amplification is beneficial in several avenues such as, listening in noise (Bhagat & Carter, 2010; Kumar & Vanaja, 2004; Mishra & Lutman, 2014), protection against acoustic injury (Rajan, 2000), localization in noise (Andéol et al., 2011), learning (Irving, Moore, Liberman, & Sumner, 2011), and for proper development of the auditory system itself (Simmons, 2002). Consid-

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ering the MOC plays a multifaceted role in the auditory system, it is imperative to understand its response to stimuli of diverse spectral and temporal characteristics. Despite the wealth of understanding of the MOCs effect for spectrally varying stimuli (Lilaonitkul & Guinan, 2009; Maison, Micheyl, Andéol, Gallégo, & Collet, 2000; Zhao & Dhar, 2012), the effect for various temporal patterns of the MOC elicitor remain unclear. Maison, Micheyl, and Collet (1999) reported an enhanced MOC inhibition of 1 kHz toneburst OAEs (TBOAEs) for broadband noise (BBN) amplitude modulated at 100 Hz/100% depth (AM-BBN), compared to unmodulated noise and other modulation frequencies (MFs) and depths (MD). AM (Maison, Micheyl, & Collet, 1997) and frequency modulated (FM: Maison, Micheyl, & Collet, 1998) tones also elicit larger MOC inhibition than unmodulated tones, but this can partially be due to increase in the elicitor-tone bandwidth caused by modulation. The bandwidth of BBN does not change with AM.

Contrary to Maison et al. (1999), Backus (2005), using stimulus frequency OAEs (SFOAEs), showed a monotonic increase in the overall MOC response as a function of elicitor MF (0.5-200 Hz). Backus (2005) also reported that the largest MOC inhibition of SFOAEs was obtained for unmodulated BBN, and no special effect for 100 Hz AM was found. Backus (2005) suggested that this is due to MOC time constants, which will be discussed further below. While the n-size in Backus (2005) study was only four, the difference between the Maison et al. (1999) and Backus (2005) findings could possibly also arise due to the use of different OAE types: TBOAEs in the former and SFOAEs in the latter. Although both TBOAEs and SFOAEs are hypothesized to be generated by the same mechanism in the cochlea (Kalluri & Shera, 2007), it is possible that differences in MOC activation could be observed, possibly due to the use of a 50 Hz toneburst (TB) presentation rate in Maison et al. (1999). It is possible that the 50 Hz rate and its harmonics, produced during the neural transduction process, may

interact with 100 Hz contralateral modulation at the neural level. Interactions are sometimes possible, as demonstrated with binaural auditory steady state responses (ASSRs) (Lins, Picton, Picton, Champagne, & Durieux-Smith, 1995). In addition, high click presentation rates (e.g., 50 Hz and above) have been shown to activate the contralateral MOC (Veuillet, Collet, & Duclaux, 1991), and hence lower rates (e.g., 40 Hz) are employed in more recent studies (Francis & Guinan, 2010). For these reasons, we cannot rule out the possibility that enhanced MOC activity at 100 Hz MF in Maison et al. (1999) may stem from the specific parameters used to evoke MOC activity and record OAEs, rather than a true MOC effect. Therefore, to investigate this rate effect further, two studies were conducted: the first study attempted to reconcile the results of Maison et al. (1999) and Backus (2005) using both SF- and TB-OAEs. TBs were specifically presented at 41.67 Hz (lower than the typical 50 Hz rate) in this experiment to minimize the possibility of the TBs evoking MOC activity by themselves (Francis & Guinan, 2010; Veuillet et al., 1991). In the second experiment, TBs were presented at 50 Hz to tease out the effect of TB presentation rate as a possible contributor to the enhanced 100 Hz AM-BBN MOC response reported by Maison et al. (1999).

2.2 Method

2.2.1 Participants

Twenty-seven young adults (18 to 30 years) participated in the studies. All participants had normal hearing, defined by normal middle ear function and hearing thresholds of 20 dB HL or better between 0.25 and 8 kHz at octave intervals. In addition, acoustic reflex threshold (ART) for steady-state BBN was required to be >80 dB HL (Guinan, 2006), measured using a clinical immitance meter (Madsen Otoflex, GN-Otometrics, Denmark). Spontaneous OAEs (SOAEs) were recorded to

allow rejection of SFOAEs within 50 Hz of an SOAE to avoid phase related complexities (Francis & Guinan, 2010). The Health Sciences Research Ethics Board of Western University, Canada approved the study methods. Written informed consent was obtained from each participant after the nature of the study was explained. Participants sat in a comfortable chair in the double walled sound attenuated booth and were encouraged to relax, swallow as few times as comfortable, and sleep if possible. The ear being tested and the order of the OAE being tested were counterbalanced across participants.

2.2.2 Stimulus generation and recording

Probe tones (f_P) in the frequency range 0.96 to 1.92 kHz (48 Hz intervals) were of 2.048s in duration and were presented at 40 dB SPL to evoke SFOAEs. To obtain SFOAEs, the suppression method (Brass & Kemp, 1993) was used with discrete Fourier transforms. Each f_P thus had a corresponding intra-cochlear suppressor (f_S) that was presented at 60 dB SPL, where $f_S = f_P + 16$ Hz with linear rise/fall ramps of 50 ms duration. Blackman-window gated TBs of frequencies 1 and 2 kHz, and 2 ms in duration were used to obtain TBOAEs (Norton & Neely, 1987). The frequency range was chosen based on empirical evidence that contralateral MOC activity is more pronounced in the 1-2 kHz region (Lilaonitkul & Guinan, 2012; Zhao & Dhar, 2012). Efferent elicitors were uniform BBN and AM-BBN (BBN modulated at 100 Hz and 100% depth) (Maison et al., 1999). Elicitors had equal root-mean-square (RMS) amplitude and rise/fall ramps of 20 ms each to avoid causing a startle response. Stimuli were calibrated using a Type-2250 sound level meter (Brüel and Kjær, Denmark) and ear simulator Type-4157 (IEC711; Brüel and Kjær, Denmark).

Signals were played through a digital-to-analog converter (6289 m-series, National Instruments, TX) at a sampling rate of 32 kHz to three separate programmable atten-

uators (PA5; Tucker-Davis Technologies, FL) that controlled the output signal levels of the probes (tones and TBs), suppressors, and elicitors. These signals were power amplified (SA1; Tucker-Davis Technologies, FL) and fed to two ER2 transducers (Etymotic Research, IL) connected to an ER-10B+ otoacoustic emission probe system (Etymotic Research, IL) that delivered the signals in the ear-canal. A single ER2 insert receiver delivered elicitors in the contralateral ear. Responses were recorded using the ER-10B+ (Etymotic Research, IL) probe system with the pre-amplifier gain set at +40 dB. The recorded signal was then bandpass filtered (Frequency Devices Inc., IL) from 0.2 to 10 kHz with further 20 dB gain. The filtered response was then digitized by an analog-to-digital converter which applied another 6 dB of gain prior to conversion (6289 m-series, National Instruments, TX). Stimulus delivery and response acquisition were controlled using custom programs developed in LabView (National Instruments, TX), similar to Purcell, Butler, Saunders, and Allen (2008).

Experiment I

Elicitor conditions for SFOAE and TBOAE were organized as illustrated in Figure 2-1A and B, respectively. At least 8 sweeps for the SFOAE, and 20 sweeps for the TBOAE measurement were obtained. A total of 2120 TBs/elicitor condition were obtained from the 20 sweeps. The inter-sweep-block interval between elicitor conditions and the inter-sweep interval between sweeps (see Figure 2-1) ensured that MOC activity reverted to baseline before it was activated again with a different elicitor (Backus & Guinan, 2007). The SFOAE measurement at every frequency started with an in-the-canal calibration of stimulus levels to produce the desired stimulus SPL in the ear-canal. A single isovoltage calibration was used for TBOAE measurements. Influence of probe-drifts was avoided with the use of interleaved short duration sweep-blocks (2.048 s for SFOAE and 2.544 for TBOAE). Prior to calculating an average SFOAE response, all epochs were evaluated offline using a discrete Fourier transform

to obtain noise metrics in a 20 Hz band just below f_P. Epochs whose noise metric exceeded the mean plus two standard deviations (SDs) were not included in the average. The SFOAE at each frequency was obtained by vector subtraction of ear-canal pressure recorded in average sweep-blocks 1 and 2 (see Figure 2-1A). Final SFOAE and inhibition magnitude were obtained by averaging SFOAE across all included frequencies.

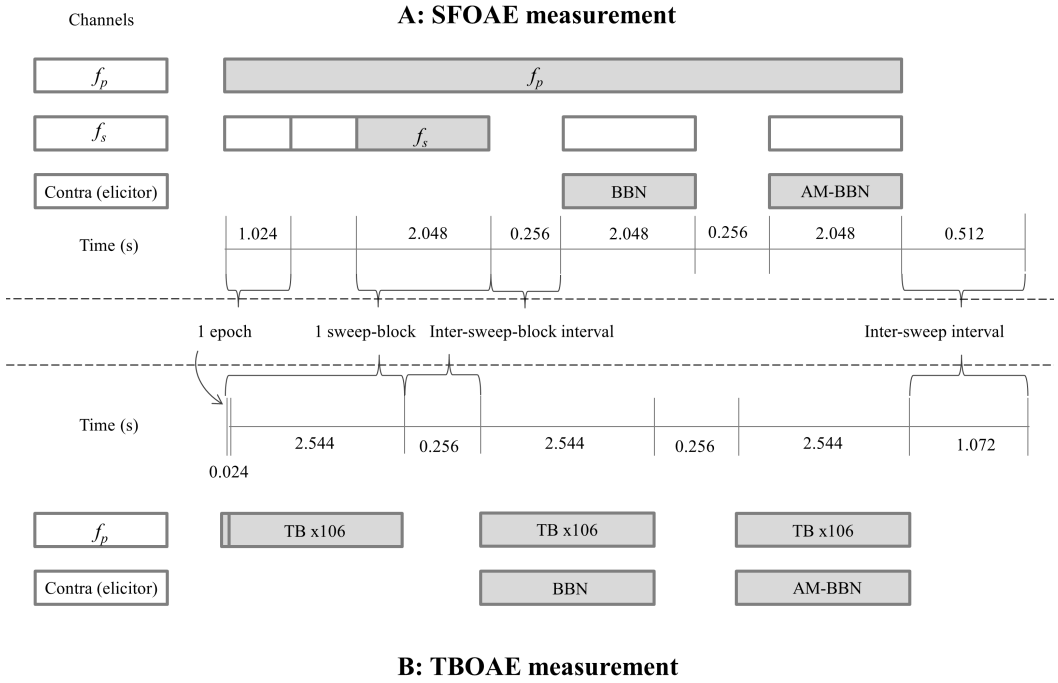

Figure 2-1: Panels A and B are block diagrams of SFOAE and TBOAE measurement paradigms, respectively. Left columns in both panels indicate the stimulus delivery channels, i.e., separate transducers. Shaded (in grey) regions represent stimulus presence.

TBOAE responses (OAEs+background noise mixture) in the time window from 8.5 to 18.5 ms post stimulus onset were extracted and digitally band-pass filtered using a fourth order Butterworth filter (cut-offs: 0.5-2 kHz for 1 kHz TB and 1-3 kHz for 2 kHz TB). Although a different time window from Maison et al. (1999)

has been used in this study, all TBOAE frequency components can be expected to be captured within this time-window, based on their latency (Shera, Guinan, & Oxenham, 2002). Consecutive TBOAE epochs were separated into two buffers (A and B); the correlation coefficient between the two buffers served as a measure of reliability. Noise and SNR for TBOAEs were calculated according to equations 2.1 and 2.2, respectively:

$$Noise = \sqrt{\frac{abs(bufferA - \bar{X})^2 + abs(bufferB - \bar{X})^2}{2}} \tag{2.1}$$

$$SNR = 10 * log10[(\frac{\bar{X}^2}{Noise^2}) - 1] \tag{2.2}$$

In equation 2.1, buffers A and B refer to the average responses in the respective buffers, and $\bar{X}$ is the mean response across both buffers. TBOAE amplitude is the mean RMS of the response within the time window.

Experiment II

Experiment II repeats Experiment I except that the TBs were presented at 50 Hz instead of 41.67 Hz. The 50 Hz TB rate was used to test if an interaction between TB presentation rate and 100 Hz AM-BBN could lead to the hypothesized enhancement in MOC inhibition for 100 Hz AM-BBN reported in Maison et al. (1999). This hypothesis was based on the ability of the auditory system to encode stimulus presentation rate, due to rectification in the cochlea and at the auditory nerve (John, Dimitrijevic, & Picton, 2003). For example, the modulation frequency of a stimulus used to elicit the ASSR is not present in the spectrum of the acoustic stimulus, but rather appears during the transduction process (Lins et al., 1995). In the present case, the neural response to the second harmonic of the 50 Hz presentation rate in the ipsilateral ear may interact with a 100 Hz AM response from the contralateral ear at

the level of the brainstem, potentially causing an enhancement of MOC inhibition for 100 Hz AM-BBN. An enhancement is hypothesized because of the potential binaural stimulation at 100 Hz MF, with reference to monaural (contralateral) stimulation alone (Berlin, Hood, Hurley, Wen, & Kemp, 1995; Lins et al., 1995).

2.2.3 Test for MEMR

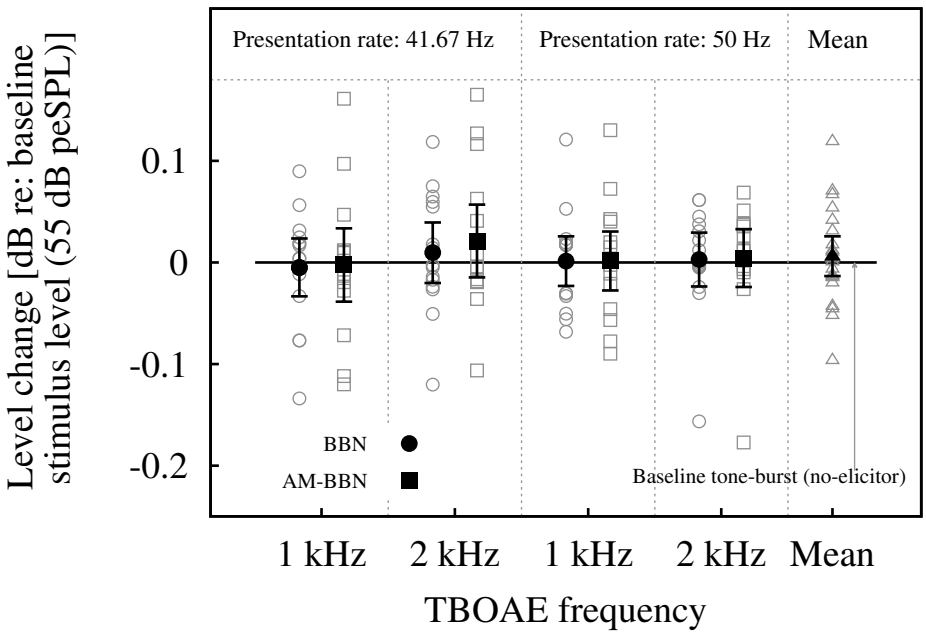

Figure 2-2: Deviations in stimulus level for all TBOAE measurements during BBN and AM-BBN presentations are plotted in dB (re: no-elicitor). Filled symbols represent group mean with error-bars representing 95% confidence interval. Grey unfilled symbols are raw data. Note that deviations in stimulus level occur in both directions from baseline across participants and are very small.

In addition to recruiting participants only with high enough ARTs (>80 dB HL), tone-burst levels were evaluated offline for deviations in level during elicitor presentations (re: no-elicitor condition). This test is based on the hypothesis that a significant MEMR would consistently increase probe-tip stimulus levels. This is because, MEMR activation will stiffen the ossicular chain and retract the tympanic

membrane, resulting in increased reflection of stimulus energy back to the ear-canal. A cut-off value of 1.4% (0.12 dB) increase in stimulus level during elicitor-on condition compared to no-elicitor condition has been suggested as an indication of MEMR activation (Abdala, Dhar, Ahmadi, & Luo, 2014; Abdala, Mishra, & Garinis, 2013).

To test for such changes in level, RMS levels in the ear-canal recorded stimulus time-window near the first trough of the tone-burst waveform (∼530 μs duration) for elicitor-on/off conditions for every participant was obtained. As seen in Figure 2-2A, changes in the presence of MOC elicitors was on average -0.004 dB ±0.013 (re: baseline no-elicitor). Observed stimulus level deviations occur in both directions, i.e., increase and decrease in level. A decrease in level would not be expected if MEMR were to affect the ear-canal recorded stimulus. The observed changes are small compared to level changes that would be expected if the MEMR was activated (Abdala et al., 2014, 2013). Notwithstanding, a repeated measures analysis of variance (RM-ANOVA) was conducted for the 41.67 Hz tone-burst stimulus condition to evaluate systematic effects of frequency (1 or 2 kHz) or elicitor (BBN or AM-BBN). Results indicate no effect of frequency (F[1,14] = 1.90, p = 0.19, $\eta^2{}_{Partial}$ = 0.12), elicitor (F[1,14] = 0.98, p = 0.34, $\eta^2{}_{Partial}$ = 0.06), and no interaction between frequency and elicitor (F[1,14] = 0.69, p = 0.42, $\eta^2{}_{Partial}$ = 0.05). The observed changes likely arise due to random fluctuations in background noise.

2.2.4 Data inclusion criteria

The following criteria were applied for data to be included in statistical analyses: an SNR of 12 dB or better, and less than 10% epoch rejection was required for both OAE types, and a minimum of 85% correlation between response buffers for TBOAE, and no large stimulus level changes in the MEMR test.

Of the 27 participants, 10 were unique to experiment I, 9 to experiment II, and 8

participants took part in both experiments. Three from experiment I and two from experiment II were rejected based on inclusion criteria. All 22 included participants were considered for SFOAE, however, for both TBOAE experiment I (41.67 Hz), and TBOAE experiment II (50 Hz) there were 15 participants.

2.3 Results

RM-ANOVAs were conducted as appropriate for Experiments I and II and are described below with Greenhouse-Geisser corrections where necessary. Post-hoc tests with false discovery rate (FDR; Benjamini & Hochberg, 1995) corrections for multiple comparisons were conducted to study the effect of each elicitor separately.

2.3.1 Experiment I

Response spectra for SFOAE and TBOAEs are plotted in Figure 2-3. Note that frequency domain representations of TBOAEs are shown in Figures 2-3B and C. Activation of MOC reduced OAE levels for both SFOAE and TBOAE. Further, A one-way RM-ANOVA with elicitor condition (no-elicitor, BBN, AM-BBN) as the independent variable and SFOAE level as the dependent variable indicated a significant effect of the elicitor ($F[1.49,\ 31.47] = 77.78$, $p<0.001$, $\eta^2{}_{Partial} = 0.79$). A similar elicitor effect ($F[1.05,\ 14.71] = 30.59$, $p<0.001$, $\eta^2{}_{Partial} = 0.69$) was obtained for TBOAEs in a 2-way RM-ANOVA with frequency (1 and 2 kHz), and elicitor (no-elicitor, BBN, AM-BBN) as independent variables, and TBOAE level as the dependent variable. No interaction between elicitor and frequency ($F[1.07,15.08] = 2.18$, $p = 0.13$, $\eta^2{}_{Partial} = 0.13$) was found, despite a significant frequency effect ($F[1,14] = 89.81$, $p<0.001$, $\eta^2{}_{Partial} = 0.86$), suggesting that 100 Hz AM-BBN did not elicit larger MOC inhibition than BBN. Post-hoc comparisons (Figure 2-3D) indicated that both elicitors caused significant reduction in both SFOAE (BBN: mean difference [MD] = 1.88,

$CI_{95\%}$ = ±0.43 dB [95% confidence interval], $t[21]$ = 9.03, p<0.001; AM-BBN: MD = 1.79, $CI_{95\%}$ = ±0.36 dB, $t[21]$ = 10.48, p<0.001) and TBOAE (BBN: MD = 1.73, $CI_{95\%}$ = ±0.82 dB, $t[14]$ = 5.70, p<0.001; AM-BBN: MD=1.58, $CI_{95\%}$ = ±0.79 dB, $t[14]$ = 5.42, p<0.001) levels (re: baseline no-elicitor). Differences between BBN and AM-BBN inhibition of TBOAEs was also significant (MD = -0.15, $CI_{95\%}$ = ±0.15, $t[14]$ = -2.62, p = 0.02), with a trend towards AM-BBN eliciting lower inhibition than BBN, contrary to Maison et al. (1999).

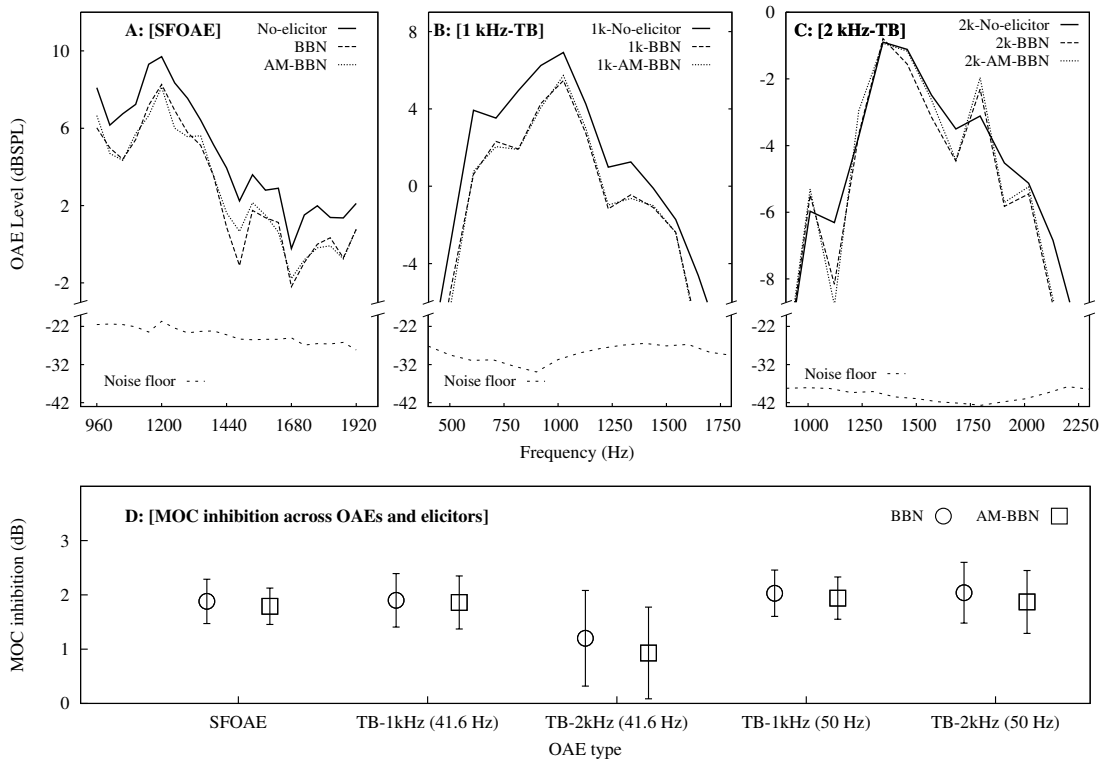

Figure 2-3: Panel A shows the grand average of SFOAE response across frequencies for all elicitor conditions. Panel B shows TBOAE for 1 kHz stimulus, and panel C shows TBOAE for 2 kHz stimulus (41.67 Hz presentation rate), for all elicitor conditions. Panel D shows mean MOC inhibition by the two elicitors for SF- and TB- OAE across frequencies and presentation rates. Error bars represent 95% confidence interval.

2.3.2 Experiment II

Results were very similar to experiment I: there was a significant effect of elicitor (F[1.08,15.17] = 69.98, p<0.001, $\eta^2_{Partial}$ = 0.83) and frequency (F[1,14] = 65.53, p<0.001, $\eta^2_{Partial}$ = 0.83), and no interaction between elicitor and frequency (F[1.3,18.21] = 1.44, p = 0.77, $\eta^2_{Partial}$ = 0.10). Results of post-hoc comparisons (see Figure 2-3D) were also similar to experiment I, i.e., BBN caused larger MOC inhibition than 100 Hz AM-BBN (MD = -0.13, $CI_{95\%}$ = ±0.12 dB, t[14] = -2.37, p = 0.03). Also, both BBN (MD = 2.03, $CI_{95\%}$ = ±0.66 dB, t[14] = 8.67, p<0.001) and AM-BBN (MD = 1.90±0.69 dB, t[14] = -2.37, p<0.001) caused significant reduction in TBOAE level.

2.4 Discussion

One of the main aims of this study was to better understand the physiology of the MOC in response to 100 Hz AM. Contrary to Maison et al. (1999), the 100 Hz AM-BBN in this study did not elicit larger OAE inhibition than BBN in both OAE types. Considering BBN and AM-BBN have the same spectral bandwidth, similar OAE inhibition may seem reasonable to expect and may be based on the modulation transfer function and time-constants of the MOC. The MOC has a ∼200 ms rise time and ∼100 ms decay time (Backus & Guinan, 2006), and its modulation transfer function suggests that at elicitor MFs higher than 1 Hz, i.e., a modulation period of 1000 ms, the MOC becomes progressively less sensitive, but not insensitive, to modulation (Backus, 2005). This is consistent with data from chinchillas, studied using distortion product OAEs, which show the MOCs ability to follow elicitor MFs until 19 Hz, i.e., a modulation period of 52.6 ms (Harrison, Sharma, Brown, Jiwani, & James, 2008). It is apparent from these studies that a modulation period of 100 Hz AM (i.e., 10 ms) may be too fast for the MOC to follow instantaneously. Despite this inability, a lower

inhibition for AM-BBN compared to BBN is observable in the current study (Figure 2-3D). This is congruous with Backus (2005), and also with Maison et al. (1999) for their 50 Hz MF. Reduced MOC inhibition for AM-BBN might occur due to energy integration across time when the response is averaged over longer periods (Maison, Durrant, Gallineau, Micheyl, & Collet, 2001). Although the elicitors RMS amplitudes were matched, the current data suggest that the increased energy at AM-BBN peaks may not be sufficient to compensate for the silent periods during modulation. The effective elicitor energy available may thus be smaller, even for faster AM rates, compared to BBN, as the MOC appears to be sensitive to AM. Modulations in noise energy may thus reduce its effectiveness in evoking MOC activity.

2.4.1 Relation between transient-stimuli presentation rate and elicitor modulation frequency

Pairwise comparisons in experiments I and II show that AM-BBN does not evoke larger inhibition than BBN for either rate. Therefore, it can be suggested that 50 Hz TB presentation rate used in Maison et al. (1999) may not be responsible for the enhanced 100 Hz AM effect reported in their study. Since the MOC does not appear to have an enhancement of MOC inhibition at 100 Hz MF, the true reason for the difference in results obtained between the present study and Maison et al. (1999) is currently unknown.

2.5 Conclusion

The current study investigated the effect of stimulating the MOC with BBN and 100 Hz AM-BBN in a sample of 22 participants (15 for TBOAE). Results suggest that AM-BBN (100 Hz MF and 100% MD) does not evoke larger MOC inhibition

compared to BBN, which is contrary to Maison et al. (1999), but in keeping with Backus (2005). Any observable differences in the MOC response between BBN and AM-BBN are likely due to differences in their temporal characteristics: constant stimulation provided by BBN as opposed to the presence of sections of the modulation period that contain no noise energy in AM-BBN. Consistency of the results across the two OAE types, and TB presentation rates strengthen these findings.

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Chapter 3

Influence of Click Presentation Rate on Medial Olivocochlear System Assays

3.1 Introduction

There is an increased interest in studying the function of the medial olivocochlear system (MOC) in recent years. This is because the MOC is thought to play a variety of roles in the auditory system such as: unmasking sounds from background noise (Giraud et al., 1997; Winslow & Sachs, 1988), protection from acoustic injury (Kujawa & Liberman, 1997; Maison, Micheyl, Andéol, Gallégo, & Collet, 2000; Rajan, 2000), aiding localization-in-noise (Andéol et al., 2011; Irving, Moore, Liberman, & Sumner, 2011; May, Budelis, & Niparko, 2004) and auditory system development (Lauer & May, 2011; Simmons, 2002). Reduced MOC functioning has been reported in auditory neuropathy/dyssynchrony (Hood, Berlin, Bordelon, & Rose, 2003), auditory processing disorders (Muchnik et al., 2004; Sanches & Carvallo, 2006; Yalçinkaya, Yilmaz, & Muluk, 2010), learning disabilities (Garinis, Glattke, & Cone-Wesson, 2008), and reading disabilities (Veuillet, Magnan, Ecalle, Thai-Van, & Collet, 2007), further emphasizing its functional importance for normal listening. Owing to the multifaceted role of the MOC in hearing, assessing its functioning has been recommended as part of a test for normal auditory function (Mishra

& Lutman, 2013). Considering the MOC forms cholinergic synapses with the outer hair cells (OHCs), studying OHC activity by measuring changes in otoacoustic emission (OAE) level serves as an effective non-invasive technique to study MOC activity. While different OAE types are available to study the MOC, the MOC inhibitory effect is not consistent across all OAE types. Inconsistencies mostly arise from differences in OAE measurement techniques (Guinan, Backus, Lilaonitkul, & Aharonson, 2003). Methods that control for complications that influence the measurement of MOC activity are necessary to accurately interpret its effect on OHC functioning.

The most commonly used OAE to study MOC functioning, both clinically and in research, is the transient evoked OAE. All clinical OAE instruments have a transient OAE module, making it the most easily accessible OAE to clinicians. Transient OAEs can be evoked using clicks or tonebursts (CEOAE or TBOAE, respectively). These OAEs are thought to be generated by coherent reflection from random irregularities along the basilar membrane (Kalluri & Shera, 2007; Shera & Guinan, 1999). Due to the broadband nature of the click, wavelets of multiple frequencies interact on the basilar membrane to produce distortion components (Withnell, Dhar, & Thomsen, 2005; Yates & Withnell, 1999). However, unlike the constructive and destructive interference seen in the ear-canal measurement of distortion product OAEs (DPOAEs; Abdala, Mishra, & Williams, 2008; Gaskill & Brown, 1996), distortion products in the CEOAE are thought to reinforce the overall emission due to their broadband nature (Yates & Withnell, 1999). Considering click stimuli are broadband, it is quicker to obtain responses from a larger region of the basilar membrane using CEOAEs. Although CEOAEs are not frequency specific, they are useful in testing gross MOC function, and a frequency specific assessment of the MOC may not be necessary in a clinical setting. Besides, the MOC itself is not frequency specific with a skew in its inhibition frequency tuning towards the 1-2 kHz region (Lilaonitkul & Guinan, 2012;

Zhao & Dhar, 2012).

However, CEOAEs have some shortcomings that are particularly relevant to MOC assays. Click levels as low as 43 dB peSPL have been shown to evoke both ipsilateral and contralateral MOC activity (Guinan et al., 2003). Many studies that have investigated the effect of click level in evoking MOC activity have used high click levels (60 dB peSPL or higher) to monitor CEOAEs in the ipsilateral ear, which may confound estimation of a true contralateral effect (Veuillet, Collet, & Duclaux, 1991). Also, rapid click presentation rates have been shown to evoke MOC activity by themselves (Veuillet et al., 1991). Veuillet et al. (1991) studied several click presentation rates and suggested that rates higher than 50 Hz, i.e., clicks that are presented less than 20 ms apart, can evoke MOC activity. A rate effect may occur due to temporal energy integration, facilitated by the broadband nature of clicks. Veuillet et al. (1991) used the click-train as an elicitor in the contralateral ear in addition to using clicks to monitor MOC activity in the ipsilateral ear.

However, if clicks were to evoke MOC activity in a typical MOC assay (i.e., OAE measurement with clicks in the ipsilateral ear and noise as the contralateral elicitor), they would evoke the ipsilateral MOC pathway, not the contralateral. The results of Veuillet et al. (1991) thus only show whether clicks presented at a given rate are sufficient to evoke contralateral MOC activity. These caveats (level and presentation rate) render the MOC effect observed with typical assays ambiguous; it cannot be ascertained if MOC inhibition was caused by the ipsilateral click-train or the contralateral broadband noise (BBN), or a binaural effect of the click-train+BBN combination. This can influence interpretation of the contralateral MOC effect. To elucidate the specific effect of click presentation rates on MOC activity, rate effects must be examined in the test/ipsilateral ear in a manner that emulates a typical

MOC test paradigm. Understanding the effect of presentation rate will provide us valuable information about MOC function, and will help us make recommendations for optimal click presentation rate for clinical use. The present study investigated the effect of click presentation rate on MOC activity using forward masking methods to maintain the stimulus paradigms as close to typical MOC assays as possible.

3.2 Method

3.2.1 Participants

Twenty eight participants (3 males) in the age range 18-30 (mean = 23.4) years took part in the study. All participants were screened for normal hearing, defined by: hearing thresholds $\leq$20 dB HL at octave intervals between 0.25 and 8 kHz, normal middle ear functioning defined by type-A tympanogram, middle ear pressure between $\pm$50 daPa and static compliance between 0.3 and 1.5 mmho (Madsen-Otoflex100, GNOtometrics, Denmark). In addition, the acoustic reflex threshold for steady state contralateral and ipsilateral BBN was required to be at least 70 dB HL to rule out middle ear muscle reflex (MEMR) as a potential cause for changes in OAE level (Madsen Otoflex-100, GNresound, Denmark). A screening CEOAE measurement (Integrity-v500, Vivosonic Inc., ON) with 55 dB peSPL clicks at 50 Hz rate was also performed to determine if participants had measurable CEOAEs. The Health Sciences Research Ethics Board of Western University, Canada approved the study methods. Written informed consent was obtained from each participant after the nature of the study was explained. Participants were compensated for their time. The study was conducted in a double walled, sound attenuated booth.

3.2.2 Stimulus generation and recording

All stimuli were digitally generated in Matlab (Mathworks, MA) at a sampling rate of 32 kHz and a bit depth of 24. Clicks were four sample points wide, i.e., 93.75 μs plateau with no rise/fall time. Uniform random BBN of 478 ms duration with 20 ms linear rise/fall ramps was used as the noise elicitor (NE) ipsilaterally, and BBN of 576 ms duration was the contralateral MOC elicitor. Signals were played through a digital-to-analog converter (6289 m-series, National Instruments, TX) at a sampling rate of 32 kHz to three separate programmable attenuators (PA5; Tucker-Davis Technologies, FL) that controlled the output signal levels. Signals were power amplified (SA1; Tucker-Davis Technologies, FL) and fed to two ER2 transducers (Etymotic Research, IL) connected to an ER10B+ otoacoustic emission probe system (Etymotic Research, IL) that delivered the signals in the ipsilateral ear. A single ER2 insert receiver delivered MOC elicitor in the contralateral ear. Stimuli were calibrated using a Type-2250 sound level meter (Brüel and Kjær, Denmark) and ear simulator Type-4157 (IEC711; Brüel and Kjær, Denmark).

Responses were recorded using the ER-10B+ probe system with pre-amplifier gain set at +40 dB. The recorded signal was fed through a bandpass filter (Frequency Devices Inc., IL) that filtered responses from 0.4 to 10 kHz and applied an additional +20 dB gain. A final gain of 2 was applied at the analog-to-digital converter (6289 m-series, National Instruments, TX). Stimulus delivery and response acquisition were controlled using custom programs developed in LabView (National Instruments, TX). All clicks were presented at 55 dB peSPL, and elicitors at 60 dB SPL. Participants sat in a comfortable chair in the sound attenuated booth and watched a closed captioned silent movie; they were encouraged to relax and swallow as few times as comfortable. OAEs were recorded from only one ear per participant. The ear being tested was chosen based on the ear with larger OAE amplitude in the screening CEOAE mea-

surement.

To describe the presentation of each stimulus, we will define the terms 'click elicitor (CE)-block', 'noise elicitor (NE)-block', 'test-block', 'sweep-block', 'sweep' and 'epoch' as illustrated in Figure 3-1. Two 'Test clicks', i.e., two epochs, were presented in each test-block at 20.83 clicks/s, and only OAEs generated by these clicks were used to study MOC inhibition.

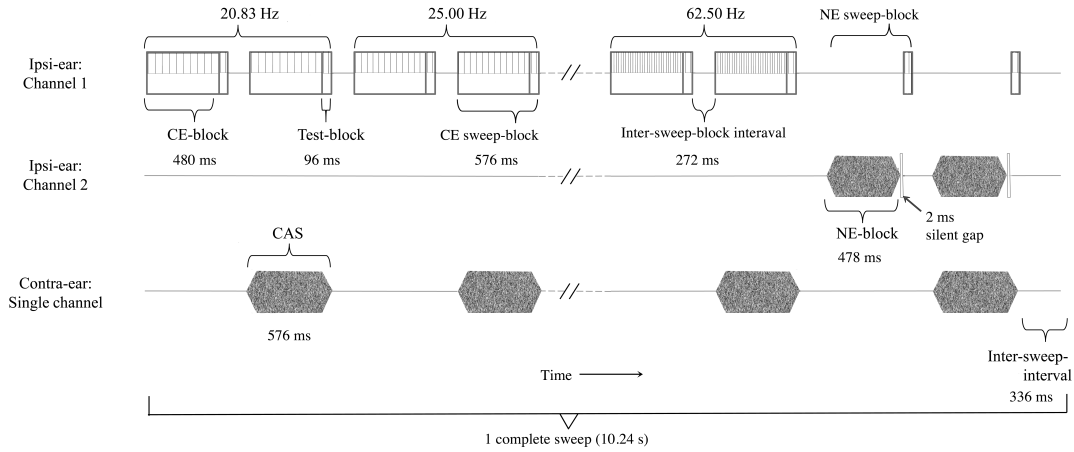

Figure 3-1: A schematic representation of the temporal order of CE-/NE-blocks and elicitor presentations. A sweep-block contains either a CE or NE block with a test-block. Every pair of sweep-blocks includes one elicitor-off and one elicitor-on condition, emulating a typical MOC assay. Duration of each stimulus element is provided in their respective labels. Baseline MOC inhibition measurement (not shown here) had similar click set-up as in the NE sweep-block but without any NE. Note that the sizes of elements in this figure are enhanced disproportionately to show shorter events more clearly.

Test-block duration of 96 ms was specifically chosen to capture MOC activity evoked by the preceding CE-block before it decayed (Backus & Guinan, 2006). A CE-block could contain clicks presented at one of five different presentation rates (20.83, 25.00, 31.25, 41.67, and 62.50 clicks/s), and had a fixed duration of 480 ms.

Therefore the number of clicks in different CE-blocks varied. The test- and CE-blocks were presented in channel-1 of the ipsilateral probe. An NE-block (480 ms) contained the NE (478 ms) and a 2 ms silent period to allow any stimulus ringing to subside and was presented in channel-2 of the ipsilateral probe. A sweep-block (576 ms) contained one NE- or CE-block and a test-block combination. Every sweep-block was followed by an identical sweep-block with contralateral MOC elicitor. This set-up emulates typical MOC assays with the CEOAE evoking clicks in the ipsilateral ear and MOC evoking elicitor in the contralateral ear. There were 12 sweep-blocks in one complete sweep: five CE+test-block combinations, and one NE+test-block combination, and their identical paired sweep-blocks with contralateral elicitor. Every sweep-block was separated by a 272 ms silent period, and every sweep by 336 ms of silence. These gaps allowed the MOC to revert back to its resting state before being activated by another elicitor (Backus & Guinan, 2006). The total duration of one sweep was 10.24 s and sweeps were repeated 700 times to obtain 1400 CEOAEs per rate and NE condition, respectively. The order of presentation of sweep-blocks (i.e., rates) was counterbalanced. Baseline MOC inhibition was obtained from the difference between mean CEOAE levels evoked by two clicks presented at 20.83 Hz in isolation and two similar clicks with contralateral elicitor in a separate sweep that was 1.024 s long, to obtain 1400 clicks for baseline CEOAEs with and without contralateral elicitor. The experiment was completed in two sessions in most participants based on participant availability.

3.2.3 CEOAE extraction

In offline analysis with Matlab, stimulus reliability was checked across all recorded epochs to remove artifactual epochs. Epochs with stimulus root-mean-square (RMS) amplitude that was two standard deviations (SD) above or below the mean (within-individual) were rejected. Responses in the time-window from 5-20 ms were extracted,

and digitally bandpass filtered from 0.5 to 6 kHz using a fourth order zero delay Butterworth filter to obtain CEOAE and noise metrics. To estimate response reliability, consecutive epochs were separated into two buffers: A and B. A correlation analysis was performed between the two buffers which served as a measure of reliability. Noise was estimated by subtracting the RMS difference between the grand response mean (mean of buffers A and B) and mean responses obtained in each buffer (A and B) separately. CEOAE level was calculated as the mean RMS amplitude of the response within the time window (5-20 ms). The MOC inhibitory response is expressed as the normalized (re: baseline CEOAE level) percent change in CEOAE level (in Pa) from baseline no-elicitor condition (ΔOAEn) to either the preceding CE-block, contralateral MOC elicitor, or a combination of CE-block+contralateral MOC elicitor conditions.

3.2.4 Test for MEMR

In addition to recruiting participants only with sufficiently high ARTs (>70 dB HL), click levels were probed offline for deviations in level during elicitor presentations (re: no-elicitor condition). This test is based on the hypothesis that a significant MEMR would consistently increase probe-tip stimulus levels. This is because MEMR activation will stiffen the ossicular chain and retract the tympanic membrane, resulting in increased reflection of stimulus energy back to the ear-canal. A cut-off value of 1.4% (0.12 dB) increase in stimulus level during elicitor-on condition compared to elicitor-off condition was suggested as a possible indication of MEMR activation (Abdala, Dhar, Ahmadi, & Luo, 2014; Abdala, Mishra, & Garinis, 2013).

To test for such changes in stimulus level, average RMS click levels in a time-window (125 μs) near the first trough of the recorded click waveform across all conditions for every participant were obtained. As seen in Figure 3-2, changes in the presence of MOC elicitors was on average -0.0036 dB (re: baseline elicitor-off). The largest

change in both directions (increase and decrease in amplitude) were ±0.06 dB (± indicates ±95% confidence interval [$CI_{95\%}$]).

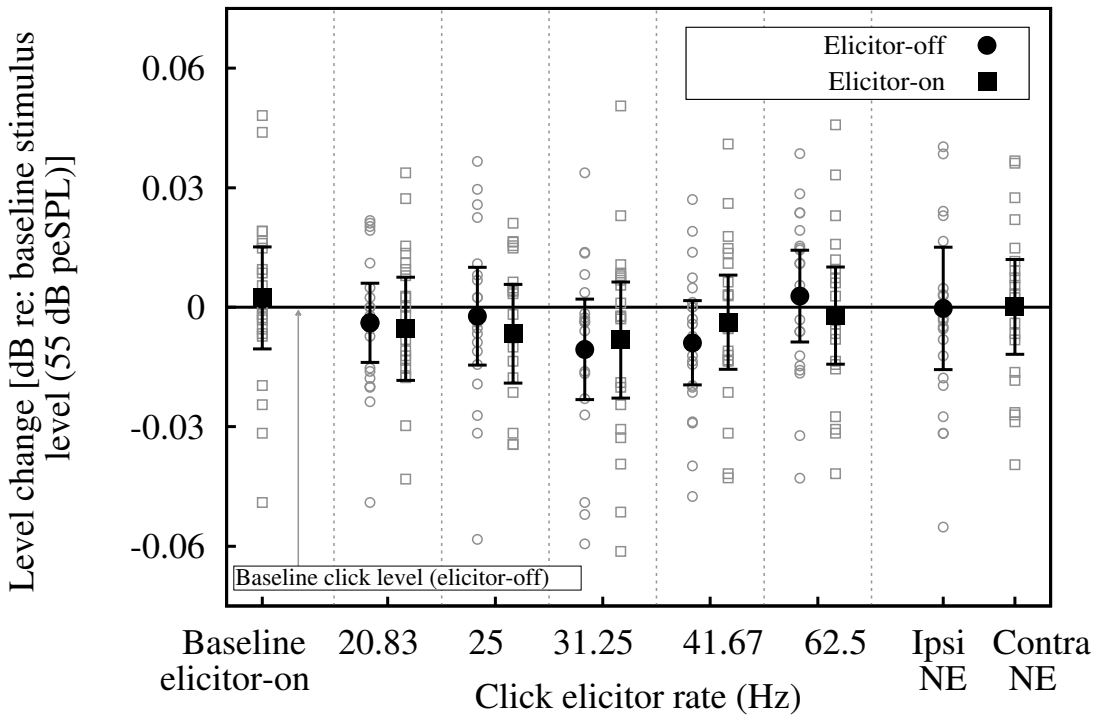

Figure 3-2: Level change in stimulus across all conditions employed in the study. Shape of the symbol indicate presence or absence of elicitor. Filled symbols in black are group mean and their corresponding error-bars represent 99% confidence interval. Open symbols in grey are individual data.

To check for systematic changes in stimulus level across conditions, a repeated measures analysis of variance (RM-ANOVA) was conducted with independent variables (1) presence of contralateral elicitor, i.e., MOC elicitor and (2) CE-block click-rate (rate), and change in stimulus amplitude as the dependent variable. Results were interpreted with Greenhouse-Geisser corrections for degrees of freedom for violation of sphericity. No interaction between elicitor (on/off) and rate (F[2.3,46.69] = 1.40, p = 0.24, $\eta^2_{Partial}$ = 0.07) was found. There was also no effect of elicitor (F[1,20] = 0.53, p = 0.82, $\eta^2_{Partial}$ = 0.003) and no effect of rate (F[3.14,62.89] = 2.64, p =

0.054, $\eta^2{}_{Partial} = 0.12$). The small changes observed in stimulus amplitude therefore did not vary significantly between with and without MOC elicitor conditions, or as a function of rate. Therefore, data from all CE-block conditions (with and without MOC elicitor) were pooled to create one variable. This CE-block variable and three NE-block variables (ipsilateral, contralateral and binaural noise presentations) were subjected to another RM-ANOVA to test for systematic changes in stimulus amplitude due to the presence of CE- or NE- blocks. These results also show no difference in stimulus amplitude changes across CE- and any NE-block conditions (F[1.9,38.63] = 0.69, $p = 0.56$, $\eta^2{}_{Partial} = 0.03$). These analyses suggest that, across participants, stimuli used to evoke MOC activity did not evoke any MEMR. The observed deflections in stimulus amplitude are likely due to random changes in noise. Therefore, we conclude that any level change reported in the present study is likely only due to the MOC, and not MEMR.

3.2.5 Data inclusion criteria

For data to be considered for statistical analysis the following criteria had to be met: (1) a correlation coefficient of 0.85 or higher was required between the two response buffers, (2) <10% epochs could be rejected, (3) a minimum signal-to-noise ratio (SNR) of 10 dB, and (4) no MEMR activation. Based on the inclusion criteria, 7 participants were rejected either due to poor SNR or excessive participant related artifacts.

3.3 Results

3.3.1 Statistical analyses

To analyze the omnibus effect of rate, repeated measures analysis of variance (RM-ANOVA) were performed. The results of RM-ANOVA were interpreted with Greenhouse-Geisser degrees of freedom corrections for violations of sphericity. Further, post-hoc

paired t-tests with alpha (0.05) correction using the false discovery rate (FDR; Benjamini & Hochberg, 1995) for performing multiple comparisons were carried out to study the effect of each rate separately.

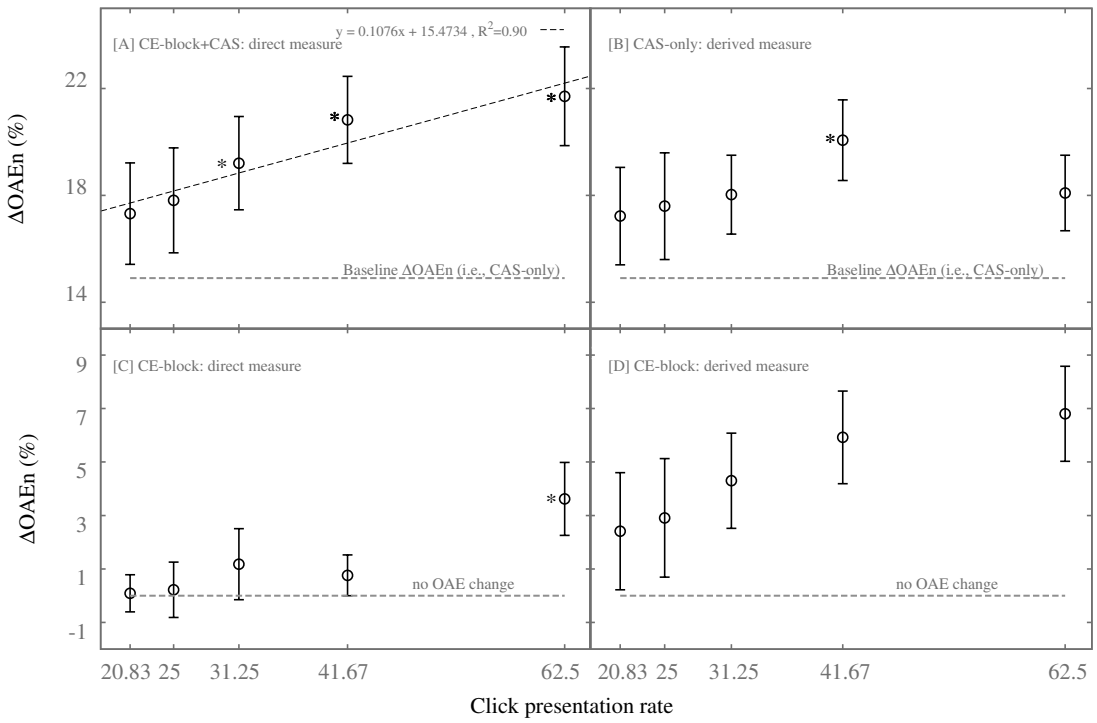

Figure 3-3: Panel [A] shows the effect of CE-block+elicitor combination on CEOAEs as a function of rate in open circles. The regression line fit is shown as a dashed diagonal line with its corresponding equation on top right corner of the box. This rate effect is compared against baseline ΔOAEn (14.9%) shown in dashed grey horizontal line. Panel [B] is the elicitor effect derived by subtracting the ΔOAEn obtained in CE-blocks with and without elicitor, compared against baseline ΔOAEn. Panel [C] is the ΔOAEn elicited by ipsilateral CE-block alone, compared against no change in OAE level depicted in the grey dashed horizontal line. Panel [D] is the ΔOAEn obtained by subtracting baseline ΔOAEn from the ΔOAEn elicited by CE-block+elicitor combination. In essence, this is the rate effect in panel A minus the baseline ΔOAEn. In all panels, asterisks represent significant mean differences between the ΔOAEn elicited by respective CE-/NE-block conditions and baseline ΔOAEn due to elicitor or preceding clicks (for C). Error bars represent 95% confidence interval.

Results are divided into two types of measures: direct and derived. A direct measure is a straightforward interpretation of the observed change in CEOAE due to MOC activation. The derived equivalent of a direct measure is ascertained from two or more direct measures.

3.3.2 Effect of CE-block+contralateral elicitor combination: Emulated typical MOC assay (*direct measure*)

The RM-ANOVA with rate as the independent variable and ΔOAEn (baseline, all rates, and NE-block+contralateral elicitor) as the dependent variable indicated a significant effect of rate as expected (F[2.41,48.27] = 43.11, $p<0.001$, $\eta^2_{Partial} = 0.68$). Post-hoc t-tests showed that click rates higher than 25 Hz in combination with the contralateral elicitor evoked significantly larger MOC inhibition than baseline inhibition caused by contralateral elicitor alone (Figure 3-3A; $t[20]$ = -1.101, $p = 0.284$ for 20.83 Hz; $t[20]$ = -1.313, $p = 0.204$ for 25 Hz; $t[20]$ = -2.417, $p = 0.025$ for 31.25 Hz; $t[20]$ = -3.419, $p = 0.003$ for 41.6 Hz; $t[20]$ = -3.829, $p = 0.001$ for 62.5 Hz).

A linear regression model fit to the CE-block+contralateral elicitor inhibition data (Figure 3-3A) shows that click rate significantly predicted MOC inhibition; in ΔOAEn (i.e., % as in Figure 3-3A): β=0.1%, $t[19] = 5.69$, $p = 0.01$; in dB: β=0.01 dB, $t[19] = 5.21$, $p = 0.01$, after correction for α using FDR for performing multiple regression analyses. Click presentation rate also explained a significant proportion of variance in the inhibition; in %: $R^2 = 0.90$, ($F[1,18] = 27.22$, $p = 0.01$) and in dB: $R^2 = 0.91$ ($F[1,18]$=32.31, $p = 0.01$). There is a near monotonic increase in the rate effect on MOC inhibition due to CE-block+contralateral elicitor combination.

3.3.3 Effect of contralateral MOC elicitor (*derived measure*)

The direct contralateral elicitor measure, or the true effect of contralateral elicitor is the baseline ΔOAEn (14.9%). However, because all CE-blocks had a elicitor-on and -off condition, simple subtraction of CEOAE levels from the two conditions would cancel out any rate effects if the MOC inhibition was linear. Therefore, remaining ΔOAEn should equal baseline ΔOAEn, i.e., it should represent the effect of contralateral elicitor only (Figure 3-3B). Results of paired t-tests show that the derived contralateral elicitor-only effect is significantly higher than baseline ΔOAEn for the 41.67 Hz condition ($t[20]$ = -3.092, p = 0.006 for 41.6 Hz); for 31.25 Hz and 62.5 Hz conditions, the mean differences approached significance ($t[20]$ = -1.948, p = 0.06 for 31.25 Hz; $t[20]$ = -2.079, p = 0.051 for 62.5 Hz). Considering the effect of rate is not completely removed by simple subtraction, this suggests that the combined effect of click presentation rate and contralateral elicitor on the MOC may be non-linear.

3.3.4 Effect of CE-block - I (*direct measure*)

The effect of CE-block, i.e., preceding clicks, obtained from test-blocks preceded by CE-blocks (elicitor-off), ranged from 0.09% for 20.83 Hz to 3.62% for 62.5 Hz (Figure 3-3C). RM-ANOVA with CE-block as the independent variable and raw CEOAE level (baseline, all rates, and ipsilateral NE-block) as the dependent variable shows a significant effect of CE-block ($F[1.74,34.86]$ = 35.77, p<0.001, $\eta^2_{Partial}$ = 0.64). Post-hoc t-tests results show that only the 62.5 Hz ($t[20]$ = 2.622, p = 0.016) and ipsilateral NE-block ($t[20]$ = 6.59, p<0.001) elicit significant MOC activity without any aid from the contralateral elicitor. MOC inhibition elicited by all NE-blocks are shown in Figure 3-4.

3.3.5 Effect of CE-block - II (*derived measure*)

Another means of obtaining the effect of preceding clicks on CEOAEs is by subtracting the ΔOAEn elicited by CE-block+contralateral elicitor combination from the baseline ΔOAEn due to contralateral elicitor alone. Linearly, if the preceding clicks independently evoked the ipsilateral pathway, this subtraction should remove the effect of contralateral elicitor and bring forth the effect of click presentation rate, as in Figure 3-3C. However, as illustrated in Figure 3-3D, ΔOAEn obtained using this method appears larger than the ΔOAEn evoked by CE-blocks alone. This finding further supports non-linear MOC activity, possibly due to binaural activation (clicks in the ipsilateral ear and MOC elicitor in the contralateral ear).

3.3.6 Effect of noise elicitor laterality

In order to test for the presence of a laterality effect, MOC inhibition obtained using ipsilateral, contralateral and binaural noise were compared. NE-blocks with elicitor-on and off provide binaural and ipsilateral MOC activations, respectively, and the baseline ΔOAEn provides contralateral MOC activation. As illustrated in Figure 3-4, contralateral elicitor evoked (i.e., baseline ΔOAEn; labeled as 'contra' in Figure 3-4) and ipsilateral NE-block evoked ΔOAEn (labeled as 'ipsi' in Figure 3-4) were not significantly different ($t[20]$ = -1.342, p = 0.19), consistent with evidence for similar MOC strengths between the contralateral and ipsilateral MOC pathways in humans (Berlin, Hood, Hurley, Wen, & Kemp, 1995; Lilaonitkul & Guinan, 2009). The binaural BBN elicitor (contralateral elicitor+NE block combination; labeled as 'binaural' in Figure 3-4) evoked significantly larger MOC inhibition (mean = 38.97%; $t[20]$ = 2.649, p = 0.01) than the sum of ipsilateral + contralateral combination (mean = 33.01%).

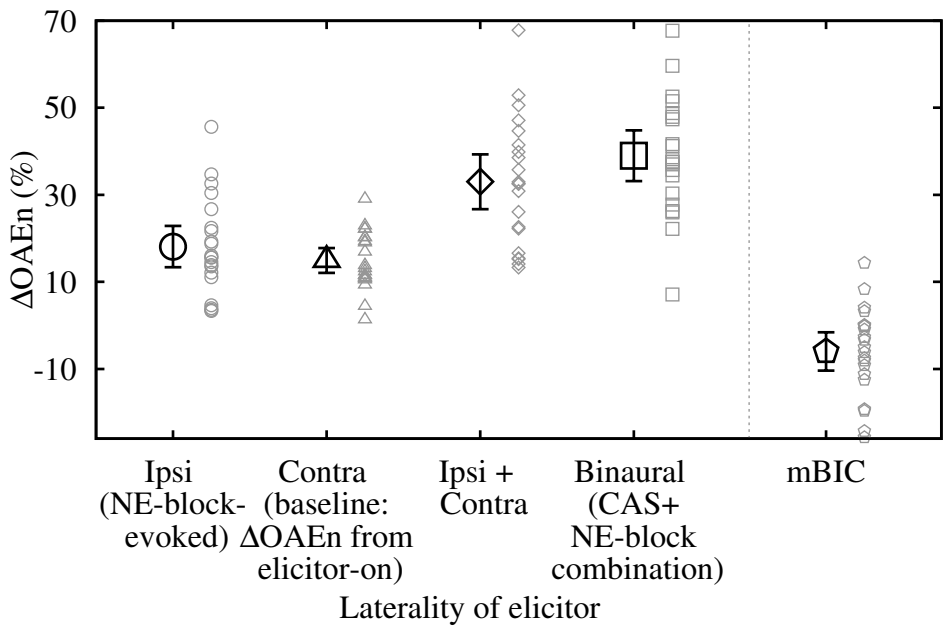

Figure 3-4: MOC inhibition of CEOAEs elicited by different NE-blocks are plotted. Symbols in black represent mean ΔOAEn for different laterlities. Accompanying symbols in grey are individual ΔOAEn for respective mean data. Error bars around the mean represrent 95% confidence intervals.

An MOC equivalent of the binaural interaction component (mBIC) was obtained from these measures (-5.96%), where mBIC is the difference between the sum of ipsilateral and contralateral inhibitions and the binaural MOC inhibition;

$$mBIC = \Delta OAEn_{Ipsi+Contralateral} - \Delta OAEn_{Binaural} \tag{3.1}$$

A negative mBIC suggests binaural facilitation, whereas a positive value would suggest inhibition of binaural inputs at the level of the brainstem.

3.4 Discussion

3.4.1 Optimal click presentation rate

The current study was undertaken to investigate click presentation rates that may enhance ΔOAEn elicited by contralateral MOC elicitor in typical CEOAE-based MOC assays. Click rates as low as 31.25 Hz significantly enhance MOC inhibition of CEOAEs, confounding the true MOC effect due to contralateral elicitors. The ΔOAEn increases near monotonically as a function of click rate, presumably due to activation of the ipsilateral and binaural MOC pathways in addition to the contralateral pathway. This rate effect can be explained based on reduced temporal gaps between stimulus clicks at high rates, and thus an increase in temporal energy integration. A similar effect on the MOC has been previously demonstrated using amplitude modulated elicitors, where MOC inhibition of OAEs increased with modulation rate (Backus, 2005). Veuillet et al. (1991) also reported increased MOC inhibition of OAEs with increasing click presentation rates.

Based on temporal energy integration, an argument for the rate effect can be made by considering intrinsic latencies of the MOC. The onset latency of the MOC ranges from 7 ms to 70 ms, and the offset latency from 20 to 81 ms (Backus & Guinan, 2006; Hill, Prasher, & Luxon, 1997; James, Harrison, Pienkowski, Dajani, & Mount, 2005; Maison, Durrant, Gallineau, Micheyl, & Collet, 2001). Of particular interest is that the MOC inhibitory effect sustains for much longer than the elicitor duration. For example, James et al. (2005) showed that the onset/offset times were 26/66 ms, respectively in chinchillas for a 5 ms long BBN MOC elicitor. It is unknown how long the MOC response is sustained for the click stimulus employed in the current study. The longer neural conduction pathway in humans compared to chinchillas leads to longer onset times in humans (45 ms) (James et al., 2005).

The MOC time-constants reported in the literature also vary across studies: 100 ms onset time-constant reported by James et al. (2005), while Backus and Guinan (2006) reported 277±64 ms. Backus and Guinan (2006) also reported a decay time-constant of 159±54 ms.

Despite differences across studies, collectively these temporal aspects of the MOC indicate that even for the lowest click presentation rate (20.83 Hz, i.e., 48 ms inter-click-interval) the MOC could be kept active due to its large time-constants. Even if the MOC does not reach saturation as evoked by a continuous noise elicitor, successive clicks would prevent the MOC from decaying to its baseline activity due to temporal energy integration (Maison et al., 2001). Therefore, for increasing click presentation rates, the temporal integration of click energy will progressively increase. However, at what rate does this integration become significant? In the current study, only click presentation rates of 31.25 Hz and higher, in combination with contralateral elicitor, significantly activated the ipsilateral and binaural MOC pathways to cause a reduction in CEOAE level. Although lower rates appear to have evoked MOC activity, evident from their numerically larger-than-baseline ΔOAEn, they were not significantly different from contralateral MOC inhibition. Nevertheless, results from the present study are in agreement with current understanding of MOC functioning, that the MOC integrates energy over time (Backus & Guinan, 2006; Berlin et al., 1995). Crucially, these results indicate that past studies that have used click presentation rates higher than 25 Hz (at click levels 55 dB peSPL or above) to study the contralateral MOC inhibition of CEOAEs would have likely evoked a combination of ipsilateral, contralateral and binaural MOC pathways. While these studies interpret that their observed CEOAE inhibition is caused by MOC activation, the MOC pathways (contralateral vs. a combination of all three pathways) responsible for the observed inhibition remain ambiguous.

Most studies that investigate the MOC using clicks have used a 50 Hz click presentation rate as a safe cut-off to avoid evoking ipsilateral MOC activity. This is probably based on the results of Veuillet et al. (1991), who reported that clicks presented at rates higher than 50 Hz are potent MOC elicitors. It should be noted that Veuillet et al. (1991) only investigated the potency of clicks presented at various rates in evoking contralateral MOC activity. Therefore, their use of clicks as contralateral elicitor does not represent a typical MOC assay. Typical MOC assays use clicks in the ipsilateral ear to monitor the MOC activity evoked by contralateral elicitor, usually BBN. In addition, the effectiveness of a given click rate evoking MOC activity in Veuillet et al. (1991) is not independent of their ipsilateral click presentation rate of 50 Hz. This is evident from the rather small ipsilateral (CE-block only) click rate effect observed for 62.5 Hz in the present study (Figure 3-3C), 0.34 dB (3.62%), as opposed to ∼0.6 dB in Veuillet et al. (1991) for contralateral clicks.

Another important parameter to consider is the level of the clicks used to obtain CEOAEs. Although the present study only investigated the effect of click presentation rate for one click level (55 dB peSPL), the effect of contralateral elicitor level on MOC inhibition is well known (Berlin et al., 1993; Collet et al., 1990). For example, Guinan et al. (2003) reported that contralateral click levels as low as 40 and up to 72 dB peSPL evoked substantial MOC activity when monitored using stimulus frequency OAEs, and sometimes even elicited middle ear muscle reflexes. However, additional tests show that MEMR was not activated in the current study (for 55 dB peSPL clicks). Veuillet et al. (1991) also reported that click levels as low as 17.5 dB sensation level (SL) evoked contralateral MOC activity, and this effect increased with further increase in click level. Veuillet et al. (1991) reported effects of click presentation rate for two different click levels: (1) constant peak level for

all click presentation rates (derived from the level required for 30 dB SL with clicks presented at 100 Hz), (2) a constant 30 dB SL for each click presentation rate. The former condition would ensure increasing overall RMS energy (i.e., increasing SPL) with increasing click rates, while the latter would cause progressive reduction in click levels (i.e., decreasing SPL). In their across-rate, constant stimulus peak level (first) condition, significant MOC inhibition of CEOAE was found for click presentation rates as low as 30.39 Hz, but significance was reached only at 50 Hz and above for the constant SL condition. Despite Veuillet et al. (1991) employing higher click levels than the current study, results of their first condition appear to be in agreement with the current data (31.25 Hz). However, it should be noted that considerable methodological differences exist between the two studies. Given that most studies typically use a 50 Hz click rate and 60 dB peSPL or higher levels to obtain CEOAE in the ipsilateral ear, it is conceivable that the observed MOC inhibition in these studies would be a combination of contralateral, ipsilateral, and binaural MOC effects. They may also evoke middle ear muscle reflexes in some ears and it is prudent to evaluate this possibility. Results from the current study and that of Guinan et al. (2003) suggest that progressively slower click rates must be used with increasing click levels.

We suggest that the widely used 50 Hz cut-off is too lenient to avoid evoking ipsilateral MOC activity in typical MOC assays. Click rates of 25 Hz or lower must be used while measuring contralateral MOC activity, at least when clicks are presented at 55 dB peSPL, to avoid contamination from ipsilateral and binaural MOC pathways. In studies where 55 dB peSPL click levels are used at rates higher than 25 Hz, a correction factor obtained from the regression model based on the current data might be used:

$$y1 = 0.012x - 0.3 \text{ (dB)} \tag{3.2}$$

$$y2 = 0.108x - 2.7 \ (\%\Delta\text{OAE}) \tag{3.3}$$

where, *y1* and *y2* are the corrections in dB and % change in CEOAE, respectively, and x is the click presentation rate (>25 Hz). The corrections would be subtracted from the obtained MOC inhibition. As this model is derived from the CE-block+contralateral elicitor combination, this correction factor will account for enhancement in MOC inhibition due to ipsilateral and binaural MOC activation, at least at 55 dB peSPL.

3.4.2 The ipsilateral effect

Inhibition of CEOAEs by the ipsilateral MOC pathway due to the use of high click presentation rates and levels may also influence CEOAE levels recorded in regular clinical evaluations (even with elicitor-off). Typically, a 50 Hz rate and 70 dB peSPL (or higher) level combination is used clinically to obtain reliable CEOAEs in a short time span (Glattke & Robinette, 2007). Results from the current study indicate that preceding clicks evoke significant MOC activity even without a contralateral MOC elicitor at rates above 41.67 Hz for 55 dB peSPL clicks. This can reduce the level of the evoked OAE. Although inhibition observed in the current study for 55 dB peSPL clicks is small (3.62%), it can be expected to be larger for clicks presented at higher levels. Use of either low click levels, a slower presentation rate, or both in combination, is prudent to obtain CEOAEs free from inhibition caused by the ipsilateral MOC pathway. However, lower click levels will in turn evoke lower CEOAE levels, and therefore may increase time taken to run the test and/or require quieter clinic rooms, for obtaining a lower noise floor. Both approaches have their trade-offs: a clinician may choose to embrace the best stimulus parameters based on individual clinic needs. Nevertheless, the use of lower click presentation rates (25 Hz) may at least reduce some, if not all, of the MOC inhibition evoked by the ipsilateral pathway

in regular CEOAE measurements.

3.4.3 The binaural effect

An interesting observation in the current study is the apparent non-linearity of the click presentation rate effect observed in both derived measures. If the ipsilateral click rate effect on the MOC were linear, a simple subtraction of CEOAE obtained from the test-blocks with elicitor-on and -off would exhibit only the inhibition due to contralateral elicitor, and therefore should be invariate across rates. The results (Figure 3-3B) indicate otherwise: MOC inhibition across rates, after removing the supposed rate effect, still displays significantly larger ΔOAEn at 41.67 Hz. In addition, the effect of CE-block (i.e., preceding clicks-only) on ΔOAEn obtained using direct and indirect methods show differences (Figures 3-3C and D). These differences may indicate some non-linearity in the MOC response. One possible reason for this non-linearity could be a rate specific binaural MOC activation. Even when the ipsilateral rate effect was removed by simple subtraction, the presentation rate may have, in combination with the contralateral elicitor, evoked binaural MOC neurons. Physiological studies have documented MOC neurons that respond specifically to binaural inputs, and monaural neurons whose responses are facilitated by binaural stimuli (Brown, Kujawa, & Duca, 1998; Liberman, 1988). Liberman (1988) reported that higher stimulus levels can activate more binaural neurons, and suggested that most MOC neurons respond to binaural inputs. Evidence for this facilitation can be observed in the current study from the negative mBIC (-5.96%). Similarly, residual MOC inhibition observed in the present study after subtracting the rate effect is thus an indication that binaural MOC stimulation occurs when higher click rates are used in typical MOC assays. These results provide further impetus for the use of low click rates while investigating the MOC using CEOAEs.

3.5 Conclusion

The current study investigated the influence of click presentation rates on contralateral MOC inhibition of CEOAEs. Rates as low as 31.25 Hz can significantly enhance MOC inhibition of CEOAEs through both ipsilateral and binaural MOC pathways. Use of click rates 25 Hz or lower is recommended for studies investigating the MOC using CEOAEs. As an alternative, correction factors for MOC inhibition of CEOAEs evoked using rates higher than 25 Hz (for clicks presented at 55 dB peSPL) have been proposed using a linear regression model of the current data. Use of lower click presentation rates is also recommended for recording CEOAEs (even without elicitor-off) in regular clinical use, to avoid activating the ipsilateral MOC pathway. As mentioned in the introduction, evaluation of MOC function is gaining attention for use as a potential diagnostic tool (Mishra & Lutman, 2013). For example, it might be useful in testing for auditory processing disorders (Muchnik et al., 2004), auditory neuropathy/dyssynchrony (Hood et al., 2003), and vulnerability to noise damage (Maison & Liberman, 2000), among others. Therefore, obtaining a reliable and unambiguous measure of MOC function is crucial. Consideration of the rate effect in future studies and clinical protocols may improve the interpretability of observed MOC inhibition of CEOAEs. Future studies that investigate the interaction of click presentation rates and levels in combination may provide broader correction factors.

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Chapter 4

Localization-in-Noise and Binaural Medial Olivocochlear Functioning in Children and Young Adults

4.1 Introduction

The ability to localize sounds requires complex processing of auditory inputs arriving at both ears. Volitional head-turn localization begins as early as four months of age (Muir, Clifton, & Clarkson, 1989), and in quiet, children as young as five years old localize with the same accuracy as adults (Litovsky, 1997; Van Deun et al., 2009). However, most studies in children are restricted to investigations of localization in the front hemifield (e.g., Litovsky & Godar, 2010; Van Deun et al., 2009), whereas localization in the median plane is scantily studied (Morrongiello & Rocca, 1987). Furthermore, in stark contrast to the adult localization-in-noise literature (e.g., Abouchacra, Emanuel, Blood, & Letowski, 1998; Good & Gilkey, 1996; Lorenzi, Gatehouse, & Lever, 1999), there is a paucity of information on localization-in-noise abilities of children. Localization helps listeners orient themselves to a desired source to attain better signal-to-noise ratio (SNR), which aids speech perception in noise (Bronkhorst, 2000; Kidd, Mason, Rohtla, & Deliwala, 1998). One physiological mechanism that is thought to aid both speech perception in noise (Kumar & Vanaja, 2004; Mishra & Lutman, 2014) and localization in noise (Andéol et

al., 2011) is the medial olivocochlear system (MOC). The MOC's unmasking function (described below) is thought to specifically aid sound localization in the median plane by unmasking spectral contrasts (Andéol et al., 2011). Considering median plane localization of speech is the most vulnerable to masking (Gilkey & Anderson, 1995), MOC activation may be invaluable in listening and localizing in noise. The present study sought to expand current literature on: (1) localization-in-noise abilities of children in the horizontal plane, including the front/back (F/B) dimension, and (2) the relationship between binaural MOC function and localization-in-noise in children.

A variety of stimuli and maskers have been used to probe localization in adults. While lateral localization of both clicks and speech is quite resilient to masking by broadband noise (BBN) (Abouchacra et al., 1998; Good & Gilkey, 1996; Lorenzi et al., 1999), F/B localization degrades at much better SNRs (Good & Gilkey, 1996). Physiologically, the strength of the response to a directional stimulus is reduced in auditory cortical neurons in the presence of noise (Brugge, Reale, & Hind, 1998; Furukawa & Middlebrooks, 2001). Noise also alters the tuning of directional maps in the superior colliculus (Martin, Vachon-Presseau, Pageau, Lepore, & Guillemot, 2010), affecting localization. Few studies have investigated the effect of complex noise such as speech-babble on localization (Hawley, Litovsky, & Colburn, 1999; Kopco, Best, & Carlile, 2010). Hawley et al. (1999) found that localization of speech sounds was relatively intact (70% correct) even in the presence of three competing sentences in a 1-of-7 loudspeaker identification task. Their results also showed that localization of a speech target did not depend on the proximity or configuration of the maskers. On the other hand, with the use of band-limited speech and low-pass filtered (both at 4 kHz) head related transfer functions (HRTF), Drullman and Bronkhorst (2000) found relatively poor localization performance (51% correct) in the presence of one to four competing talkers in a 1-of-5 loudspeaker identification task.

Simpson, Brungart, Iyer, Gilkey, and Hamil (2006) reported that detection and lateral plane localization of speech did not degrade significantly even with five competing speech maskers. However, localization performance in the median plane degraded systematically with increase in the number of maskers, independent of masker and target speaker sex. Localization performance thus degrades well before the signal becomes inaudible. It is also evident that, irrespective of masker type, median plane localization is most vulnerable to the detrimental effects of noise. This is particularly relevant for speech sound localization, considering speech has a low-pass characteristic, and high-frequency cues that provide information about median plane location can be most effectively masked (Best, Carlile, Jin, & van Schaik, 2005; Bronkhorst, 1995; Butler & Helwig, 1983; Gilkey & Anderson, 1995). Also, all the aforementioned studies have investigated the effect of masker configuration on speech localization, but the effect of a diffuse noise field has not yet been investigated.

Children require higher SNRs to achieve optimal speech intelligibility compared to adults. Bradley and Sato (2008) reported that younger children (grade-I) required 15.5 dB SNR to achieve 95% correct scores in speech intelligibility tests, while older children (grade-VI) required only 8.5 dB SNR. Since most of a child's learning takes place in school, which can have SNRs as low as -7 dB in some cases (Crandell & Smaldino, 2000; Crukley, Scollie, & Parsa, 2011), mechanisms that help children achieve better speech intelligibility will promote better learning. Good binaural hearing and localization will help children achieve better SNRs in adverse listening conditions by promoting orientation towards desired signals.

Development of localization begins very early. Volitional sound localization begins at 4 months of age, with a suppression of the reflexive sub-cortex based localization

which dominates 0-1 month (Muir et al., 1989). Ashmead, Davis, Whalen, and Odom (1991) reported that infants in the age range 16-28 weeks were able to discriminate click ITDs as small as 50-75 μs. They also showed that minimum audible angle (MAA) decreased rapidly from 20° at 20 weeks to 10° at 48 weeks in infants, and by 18 months MAAs decreased to 4° (Morrongiello, 1988). In the median plane, infants' localization improved from an MAA of 15° at six months to $4-6°$ by 18 months (Morrongiello & Rocca, 1987). The accuracy of median plane localization is typically less (4°) than the accuracy of lateral plane localization (1°) even in adults (Perrott & Saberi, 1990). By 5-6 years of age, children localize in quiet at adult levels, in the frontal hemi-field (Litovsky, 1997; Lovett, Kitterick, Huang, & Summerfield, 2012; Van Deun et al., 2009). It should be noted that most localization studies in school age children are restricted to investigations in the front hemi-field (e.g., Litovsky & Godar, 2010; Van Deun et al., 2009). Little is known about children's localization ability in the median plane.

Furthermore, despite several studies on localization in quiet (Grieco-Calub & Litovsky, 2010, 2012; Litovsky, 1997; Van Deun et al., 2009), to our knowledge, there are no studies on the localization-in-noise abilities of school age children. However, investigators have explored the concept of spatial release from masking (e.g., Litovsky, 2005; Litovsky & Ashmore, 1997). Spatial release from masking is the apparent improvement in speech perception when target speech and masking noise are spatially separated (Hawley, Litovsky, & Culling, 2004; MacKeith & Coles, 1971). Spatial release from masking taps localization abilities as well as other processes such as the head-shadow effect, binaural summation and extraction of ITD cues from the masker envelope (Litovsky, 2012). Children as early as three years of age are able to exploit the spatial separation of speech and noise to parse a desired source from noise and achieve better speech intelligibility (Garadat & Litovsky, 2007; Johnstone &

Litovsky, 2006; Litovsky, 2005). The present study, however, focused on extending current knowledge of the speech-sound localization abilities of children in BBN and speech-babble (SB) maskers. Two different maskers were used to explore whether children perform at adult levels when the target is masked by an energetic masker (BBN), and informational masker (SB). In the first part of this study, both lateral and F/B localization were investigated in children (between 7 and 16 years), and compared with young adults.

In the second part of the study, the relationship between localization-in-noise and the function of the binaural medial olivocochlear system (MOC) was investigated. The rationale behind this study is based on evidence that the MOC may aid localization-in-noise (Andéol et al., 2011; May, Budelis, & Niparko, 2004). Andéol et al. (2011) reported a significant correlation between contralaterally evoked MOC strength and median plane localization-in-noise in human adults. This relationship is thought to be related to hypothesized MOC unmasking (Guinan & Gifford, 1988; Kawase, Delgutte, & Liberman, 1993; Liberman & Brown, 1986). Due to its cholinergic inhibitory action on cochlear outer haircell (OHC) activity, the MOC is thought to improve the dynamic range of afferent auditory neurons. This improved dynamic range is thought to aid afferent neurons in firing for novel transient stimuli such as speech (Guinan, 2006). Thus far, only the relationship between the contralaterally evoked MOC and localization-in-noise has been investigated. The contralaterally evoked MOC response involves only uncrossed olivocochlear fibers. Crossed fibers cross the midline and feed back to the same ear that was acoustically stimulated, while uncrossed fibers supply the contralateral cochlea without crossing the midline (Warr, 1992; Warr & Guinan, 1979).

Methodologically, there are challenges involved in separating the MOC reflex mon-

itoring probe, typically otoacoustic emissions (OAEs), from the MOC-activating stimulus in the ear-canal while measuring the crossed MOC reflex. However, MOC inhibitory activity decays with a lag of at least 100 ms (Backus & Guinan, 2006). This small time-window can be used to capture the response of the crossed MOC reflex in the ipsilateral ear without significant signal related complications. Although uncommon, several investigators have used this method to study ipsilateral and binaural activation patterns of the MOC (Berlin, Hood, Hurley, Wen, & Kemp, 1995; Lilaonitkul & Guinan, 2009; Tavartkiladze, Frolenkov, & Artamasov, 1996). Understanding binaural MOC function and its relationship to localization-in-noise is critical because most neurons in the MOC are sensitive to binaural stimulation, and 5% of MOC neurons only respond to binaural stimuli (Liberman, 1988; Warr, 1992).

Binaural activation of the MOC may also be critical for proper signal encoding in the afferent auditory system because asymmetry in inhibition of cochlear activity may lead to subtle differences in cochlear outputs (Francis & Guinan, 2010). Francis and Guinan (2010) showed that the MOC-mediated inhibition of OHC activity alters cochlear filter widths, and consequently their delay. Therefore, if the MOC were to activate the two cochleae differently, it could alter the balance in interaural timing which could potentially impact localization. Although there is no direct evidence for this hypothesis, Darrow, Maison, and Liberman (2006) showed that selective destruction of the lateral olivocochlear neurons (LOC), another member of the periolivary group of neurons to which the MOC belongs, altered ILD sensitivity in a mouse model. Moreover, real life listening invariably comprises binaural acoustic stimulation; contralateral-only stimulation seldom takes place. Therefore, understanding binaural MOC function may provide further insights into the relationship between MOC function and localization-in-noise in both children and adults. Further, although the MOC is mature at birth (Abdala, Mishra, & Garinis, 2013), functional

use of the MOC in everyday tasks, such as localization, varies considerably across individuals (Andéol et al., 2011). Acoustic activation of the MOC is also modulated by corticofugal connections (Khalfa et al., 2001; Perrot et al., 2006) in a task-dependent manner (de Boer & Thornton, 2007; Garinis, Glattke, & Cone-Wesson, 2011; Maison, Micheyl, & Collet, 2001). Consequently, differences between adults and children in allocation of attentional resources during listening tasks (Allen & Wightman, 1994; Newman, 2009) may provide further insights into the relationship between behaviorally measured localization-in-noise and MOC strength.

In the present study, ipsilateral, contralateral and binaural MOC inhibition of click-evoked OAEs (CEOAEs) was measured in a forward masking paradigm. Further, considering it has been suggested that the MOC exhibits interaction of binaural inputs (Backus & Guinan, 2006), and since localization also involves interaction of binaural inputs, to allow direct comparison of MOC function and localization, an MOC equivalent binaural interaction component (mBIC)[1] was derived from the MOC inhibition measured with the three elicitor lateralities tested. The mBIC was defined as the difference between the MOC inhibition of CEOAEs evoked by a binaural elicitor and the sum of the two monaural inhibitions evoked by ipsilateral and contralateral elicitors. The mBIC measure was subjected to correlation with localization-in-noise ability to understand the role of binaural MOC interaction in localization-in-noise.

[1]It should be noted that the mBIC obtained here is from ipsilateral and contralateral MOC inhibition of CEOAEs, but not from right and left ears that is typical in the evoked potential literature (Dobie & Norton, 1980). Although analogous, they are not the same, because the pathways evoked by ipsilateral and contralateral MOC elicitors are different, crossed versus uncrossed, respectively. Whereas, scalp recorded afferent responses evoked by left or right ear stimulation evoke similar pathways on both sides.

4.2 Method

4.2.1 Participants

Twenty one children (7-16 years; mean: 11.4 years; 13 females), and twenty one young adults (18-30; mean: 22.8 years; all females) took part in the study. Participants were screened for normal hearing; defined by hearing thresholds within 20 dB HL between 0.25 and 8 kHz, normal middle ear function defined by a type-A tympanogram, middle ear pressure between ±50 daPa, and static compliance between 0.3 and 1.5 mmho. In addition, the ipsilateral and contralateral acoustic reflex thresholds (ART) for BBN were required to be >70 dB HL (Madsen Otoflex-100, GNotometrics, Denmark). Participants also underwent a screening distortion product OAE (DPOAE) measurement (Integrity-v500, Vivosonic Inc., ON) to confirm the presence of OAEs. The nature of the study was explained prior to obtaining a written informed assent from every child participant and an informed consent from adult participants and child participants' parents/care givers. Participants were compensated for their time with gift cards/cash towards books or school supplies. The Health Sciences Research Ethics Board of Western University, Canada approved the study methods.

4.2.2 Part I: Localization experiment

The experimental set-up of loudspeakers for the localization experiment is illustrated in Figure 4-1. The experiment was conducted in an hemi-anechoic chamber (Eckel Industries, ON, Canada). Targets were presented from 8 loudspeakers placed 45° apart in the presence of a diffuse noise field. Participants stood at the center of the loudspeaker array facing the 0° azimuthal loudspeaker.

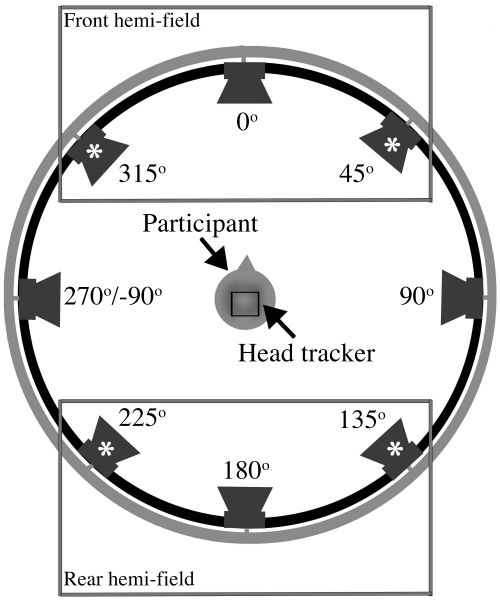

Figure 4-1: Schematic representation of the loudspeaker array for the localization experiment. Maskers were presented simultaneously through four loudspeakers placed just beneath the loudspeakers marked with asterisks. Participants stood in the center of the circular array, the radius of which was 1.5 m. The electromagnetic head tracker transmitter was positioned above and behind the participant's head, and the tracker sensor was mounted on a custom made plastic helmet worn by the participant.

Stimulus

The target stimulus was a 600-ms long speech token ('baseball') spoken by a native Canadian speaker from south-western Ontario (Grieco-Calub & Litovsky, 2012). The speech token was recorded in a sound attenuated audiometric booth using a studio-grade AKG condenser microphone (Type C 4000B) at 44.1 kHz, and later up-sampled to 48.828 kHz using Praat (Boersma, 2002) to match the sampling rate of the localization system. This speech target was chosen because of its relevance to the real world and the fact that F/B confusions occur more often with speech, compared to broadband or click targets (Gilkey & Anderson, 1995). The word baseball, however, contains both high- and low-frequency cues. Maskers were BBN (uniform and

random) and SB. SB was created by concatenating two sentences from the HINT sentence corpus (Nilsson, Soli, & Sullivan, 1994). Four different sentences pairs formed a four-channel masker that was simultaneously presented at sampling rate of 44.1 kHz in free-field using loudspeakers positioned at azimuths of 45°, 135°, 225°, and 315° (loudspeakers marked with asterisks in Figure 4-1). This set-up produced a diffuse noise field that avoided the effect of masker location on the obtained localization responses (Lorenzi et al., 1999). Similarly, BBN was presented from the same four loudspeakers during the BBN noise condition. The use of two different loudspeaker arrays to present noise and speech targets avoided any electrical mixing of signals. Maskers were looped continuously for a single block duration.

Each block, obtained by roving the target level in random order, contained 40 stimulus presentations (trials) at three different SNRs (-12, -6, and 0 dB). Three such blocks were completed for each participant for each masker condition to obtain 5 responses per SNR condition for every azimuth. In total, there were 120 trials (8 speakers x 3 SNRs x 5 repetitions). One block of trials was performed in quiet to obtain baseline localization ability.

The target was presented from any one of the 8 loudspeakers placed 45° apart, starting at 0° in a 16-channel loudspeaker array (see Figure 4-1). Using a reference microphone placed at center of the array, the root-mean-square (RMS) amplitudes of the maskers were matched, and were presented constantly with a combined level of 66 dB SPL throughout the experiment. Each target stimulus presentation was initiated by a button press by the investigator standing outside the loudspeaker array, with the participant facing the 0° azimuth loudspeaker. All stimuli were calibrated using a Type-2250 sound level meter (Brüel and Kjær, Denmark) with the microphone placed at ear level in the center of the loudspeaker array. A potential caveat in the use of a single target is that the task may be easier than real life localization of speech. On the other hand, especially in children, using a single target reduces uncertainty and

may avoid the use of high level cognition-based processes for the task.

Instrumentation

Maskers were played through a multi-channel sound interface (Audiofire12; Echo Digital Audio Corp., CA) to four separate channels of a networked signal processor (SoundWeb9008; BSS Audio, Hertfordshire, UK) which was amplified by CX18 amplifiers (QSC Audio, CA) before being fed to four Tannoy i5AW loudspeakers placed just below the loudspeakers marked with asterisk in Figure 4-1. The speech target was played through a real-time signal processor (RX6; Tucker-Davis Technologies, FL) for digital-to-analog conversion before following the same (equipment) route as the maskers, and finally to one of eight loudspeakers. Participants stood in the middle of the loudspeaker array on an adjustable stand, such that the target loudspeakers were at ear level. They were fit with a custom-made adjustable plastic helmet with a focused red LED light beam that guided them in pointing to the response azimuth. Participants were instructed to turn their head and point the red LED light to the loudspeaker from which they thought the word 'baseball' had emanated. The helmet also carried a sensor for an electromagnetic head tracker device (Frastrak, Polhemus, VT) that recorded the head position with reference to 0° azimuth. Head position was recorded upon a button press by the investigator using a custom-made response box. The head-tracker was connected through a serial data line to a head tracker interface (HTI3; Tucker-Davis Technologies, FL), which then fed the data to the RX6 real-time signal processor via a fiber optic connection. The button box was directly connected to the RX6; together, the button-press and the corresponding azimuth information was stored in a personal computer.

Measures to quantify localization ability

Example localization data obtained from a child participant are shown in Figure 4-2. Two measures were obtained to quantify the localization performance of each participant in each listening condition. The first was F/B percent correct (FBpc), which is the percentage of correct identification of sounds arriving from the front or rear hemifields. To calculate FBpc, only the responses to targets with azimuths between -67.5° to 67.5° (front hemifield) and between 112.5° to 247.5° (rear hemifield) were considered, illustrated as boxes in Figure 4-2A. The FBpc measure provides an estimate of F/B percent correct responses within the correct hemi-field, independent of the accuracy of the response. FBpc was used instead of an overall localization error because: (1) lateral angle localization is resilient to noise, and it is median plane localization that is most affected (Good & Gilkey, 1996), especially for a speech target, (2) A metric based on RMS azimuthal error (example: Abouchacra et al., 1998; Good & Gilkey, 1996; Van Deun et al., 2009) is not informative about the type of error, i.e., F/B vs. lateral.

The second measure was lateral scatter (Lscat), which is the RMS angle difference between every response and a linear regression model fit to the data. To calculate this measure, response and target azimuths from both hemi-fields (Figure 4-2A) were reduced to their lateral-angle (left/right) components lying between $-90°$ and $90°$ (Figure 4-2B), i.e., one hemi-field. This is akin to folding Figure 4-2A horizontally at $90°$ on the y-axis and vertically at $90°$ on the x-axis along the dark-grey dashed lines to reflect each target and response azimuth into the frontal hemisphere (as shown in Figure 4-2B). This measure estimates the mean consistency of responses across trials.

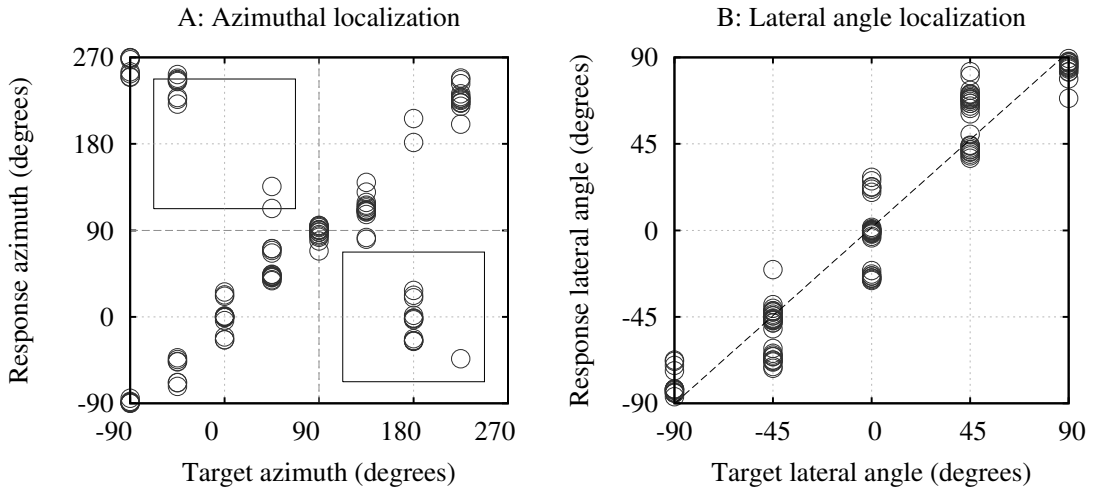

Figure 4-2: Example of localization data from a child participant and analysis methods. The plot on the left [A] shows responses to all tested azimuths on the y-axis and their corresponding target azimuths on the x-axis. Responses on or within the small black boxes are counted as F/B errors. The plot on the right [B] shows only the lateral-angle (L/R) components of the target and response locations, and is essentially a re-formatted version of A, such that if A were folded along the dashed lines running through its center, it would place rear and front hemi-fields in one quadrant. The RMS distance of individual responses from this line provides an estimate of Lscat.

4.2.3 Part II: MOC experiment

Experimental set-up: summary

The organization and temporal sequence of stimulus presentation for the MOC experiment is illustrated in Figure 4-3. Clicks (OAE evoking stimuli) and elicitors (MOC evoking stimuli) were presented in different channels. The ipsilateral probe consisted of two channels, one for clicks and one for the ipsilateral elicitor. Clicks were presented in trains of four at a rate of 41.67 Hz encompassing a duration of 96 ms; we call this arrangement a 'sweep-block'. Elicitors always preceded these 'sweep-blocks' such that they activated the MOC, and the inhibitory effect of the MOC was probed by the CEOAEs evoked by the clicks that followed. Adequate silent gaps were intro-

duced between each MOC activation so that the MOC reverted back to its baseline activity before being activated by another elicitor. A minimum duration of 200 ms is required (Backus & Guinan, 2006). The difference in this gap duration across sweep-blocks is to accommodate integer number of 1.024 s windows in one complete sweep, to match the restrictions of our measurement system. MOC inhibition of CEOAEs is the reduction in CEOAE level in any of the elicitor conditions from its baseline no-elicitor condition (the first and last sweep-blocks in Figure 4-3).

Stimulus generation and recording

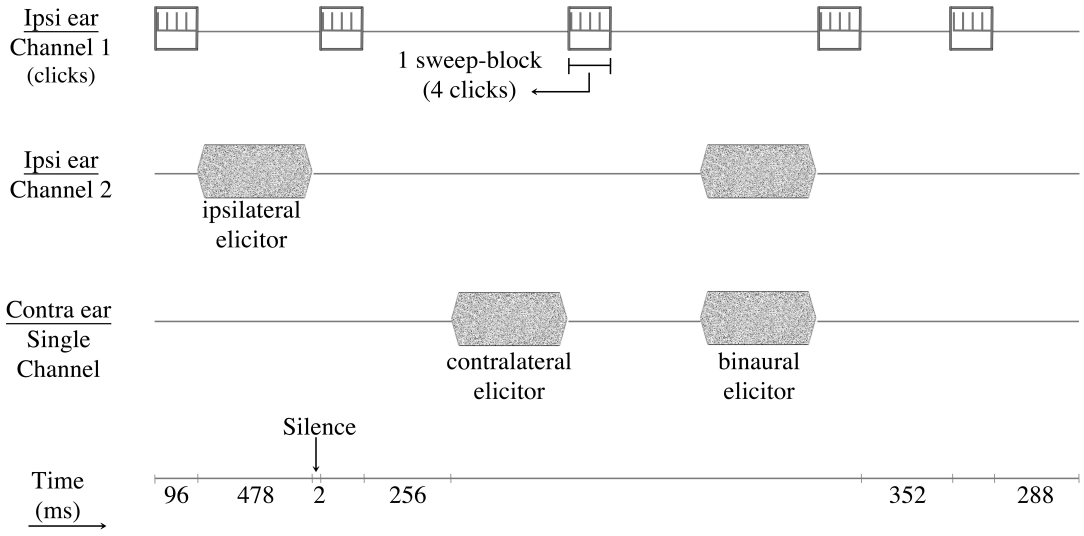

Figure 4-3: Schematic representation and temporal sequence of events for CEOAE recording with MOC elicitors. Four clicks per elicitor condition were presented to obtain CEOAE, this is depicted as squares (with clicks) on the top row. Elicitors in ipsilateral and contralateral channels are in illustrated in separate rows. Duration of each event is provided in the fourth row. Note that size of each element in the figure is made disproportionate to their duration to show shorter events clearly.

All stimuli were digitally generated in Matlab (Mathworks Inc, MA). Clicks were unfiltered, 93.75 μs in duration (corresponding to four sample points at the 32-kHz sampling rate), and were presented at 55 dB peSPL. This level was chosen to maximize

the probability of MOC-mediated CEOAE inhibition while minimizing any ipsilateral MOC inhibitory effects on CEOAE due to the evoking signals (the clicks) themselves (Hood, Berlin, Hurley, Cecola, & Bell, 1996; Veuillet, Collet, & Duclaux, 1991). The sweep-block duration was designed to capture the complete MOC inhibitory effect, which has been shown to have a decay time of 159 ± 54 ms (Backus & Guinan, 2006).

MOC activating elicitors were bursts of uniform random broadband noise (BBN) of 478-ms duration with 20-ms onset/offset ramps to avoid startle responses. Elicitors were presented at 60 dB SPL, below the acoustic reflex threshold of every participant. Notwithstanding, additional tests were performed to check for an effect of the middle ear muscle reflex (MEMR) on click stimuli (see section 4.2.3). A 2-ms gap between elicitor presentation and the start of click presentation was introduced to allow any transducer ringing to subside, and for the basilar membrane to revert to baseline activity, thus avoiding intracochlear suppression. In this forward masked CEOAE paradigm, elicitors were presented ipsilaterally, contralaterally and binaurally (see Figure 3). Signals were played through a digital-to-analog converter (National Instruments 6289 m-series, TX) at a sampling rate of 32 kHz to three separate programmable attenuators (PA5; Tucker-Davis Technologies, FL) that controlled output signal levels.

Clicks and ipsilateral elicitors were presented in two separate channels routed to the same ear. These signals were power amplified (SA1; Tucker-Davis Technologies, FL) and fed to ER2 transducers (Etymotic Research, IL) connected to an ER-10B+ otoacoustic emission probe system (Etymotic Research, IL) that delivered signals in the ear-canal. A single ER2 insert receiver delivered elicitors to the contralateral ear. All stimuli were calibrated using a Type-2250 sound level meter (Brüel and Kjær, Denmark), and an ear simulator Type-4157 (IEC 711; Brüel and Kjær, Denmark).

Responses were recorded using the ER-10B+ probe system with the pre-amplifier gain set at +40 dB. The recorded signal was then fed through a bandpass filter (Frequency Devices Inc., IL; chassis 90IP with a 90PF dual-channel programmable filter card) that filtered responses from 0.4 to 10 kHz and applied a further 20 dB gain. The filtered response was then digitized by an analog-to-digital converter which applied another 6 dB of gain prior to conversion (National Instruments 6289 m-series). Stimulus delivery and response acquisition were controlled using custom programs developed in LabView (National Instruments, TX), similar to Purcell, Butler, Saunders, and Allen (2008). The laterality of MOC elicitor presentation was counterbalanced between participants. Participants sat in a comfortable chair in a double-walled sound attenuated booth and watched a silent closed captioned movie. They were encouraged to relax and to swallow as few times as comfortable. OAEs were recorded from only one ear per participant. The ear being tested was chosen based on DPOAE amplitude obtained during a screening process.

CEOAE offline analyses

To ensure stimulus reliability, all ear-canal recordings of click stimuli were checked to remove artifacts. Epochs (each click plus its corresponding CEOAE, 24 ms duration) with RMS amplitudes that were two standard deviations (SD) above the mean (within-individual) were rejected. Following which, responses in the time-window from 5-20 ms following every click presentation were extracted and digitally bandpass filtered from 0.5 to 6 kHz using a fourth order, zero delay Butterworth filter to obtain CEOAE and noise metrics. Prior to obtaining CEOAE levels, an estimate of CEOAE reliability was calculated. For this, alternating click epochs across sweeps were collected into two buffers: A and B. A correlation analysis was performed between the two buffers that served as a measure of reliability. Noise was estimated

by subtracting the RMS difference between the grand response mean and mean responses from each buffer. CEOAE level was calculated as the mean RMS amplitude of the response within the time window. The MOC inhibitory response is expressed as normalized (re: baseline CEOAE level) percent change in CEOAE level (ΔCEn) due to MOC activation by the elicitors.

Test for MEMR

In addition to recruiting participants only with high enough ARTs (>70 dB HL), click levels were probed offline for deviations in level during elicitor presentations (re: no-elicitor condition). This test is based on the hypothesis that a significant MEMR would consistently increase probe-tip stimulus levels. This is because, MEMR activation will stiffen the ossicular chain and retract the tympanic membrane, resulting in increased reflection of stimulus energy back to the ear-canal. A cut-off value of 1.4% (0.12 dB) increase in stimulus level during elicitor-on condition compared to no-elicitor condition has been suggested as an indication of MEMR activation (Abdala, Dhar, Ahmadi, & Luo, 2014; Abdala et al., 2013).

To test for such changes in level, RMS levels of the ear-canal recorded stimulus in a time-window (125 μs wide) near the first trough of the recorded click waveform across three elicitor-on conditions for every participant were obtained. Individual and mean level-change data are plotted in Figure 4-4, which clearly shows that the deviations in stimulus level do not exceed $\pm$0.06 dB, with the largest mean deviation being -0.005$\pm$0.01 dB ($\pm$ indicates 95% confidence interval [$CI_{95\%}$]) in the ipslilateral elicitor condition.

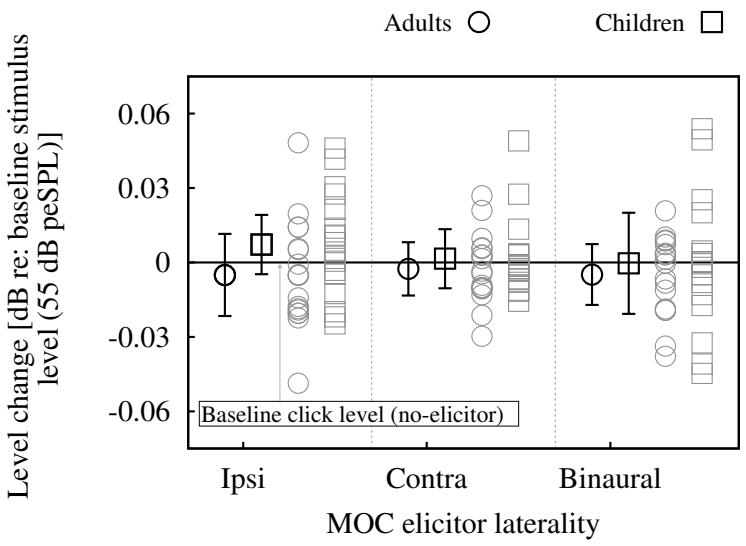

Figure 4-4: The result of MEMR test. The black straight line at 0 dB represents the baseline stimulus level change (in the no-elicitor condition). The plotted data for every elicitor condition is the dB change in level from baseline. Black symbols are group means with their corresponding 95% confidence intervals. Grey symbols are individuals means of RMS amplitude around the stimulus peak. Circles represent adults and boxes represent children.

Observed deviations are very small, and are seen in both directions, i.e., increase and decrease in level. A level reduction would not be expected if MEMR were to act on the stimulus (Abdala et al., 2013). Further, a one-way repeated measures analysis of variance (RM-ANOVA) was conducted to test for any effect of MOC elicitor laterality. If there was an effect of MEMR, a larger reduction in stimulus level in the binaural elicitor condition would be expected, compared to the two monaural lateralities, due to increased stimulus energy resulting from binaural summation. However, results show no effect of MOC elicitor laterality ($F[2,68] = 0.56$, $p = 0.58$, $\eta^2_{Partial} = 0.02$), suggesting that the observed changes in stimulus levels are not due to MEMR. These changes probably arose due to random fluctuations in the noise floor. Therefore, any CEOAE level reduction reported in this study is likely due only to MOC activation, rather than to MEMR activation.

Data inclusion criteria

For data to be considered in statistical analyses, the following criteria had to be met: (1) a correlation coefficient of 0.85 or higher between the two CEOAE response buffers, (2) <10% epoch rejection, (3) minimum SNR of 10 dB, and (4) no MEMR activation. Four participants were rejected from the child group and three participants from the adult group for the MOC experiment analyses due to poor SNR. None of the participants had MEMR activation. All participants were included in the localization experiment analyses.

4.3 Results

4.3.1 Part I: Localization

Figure 4-5 shows individual localization data (FBpc [top panel] and Lscat [bottom panel]) for all SNRs as a function of age. Larger FBpc and smaller Lscat indicate good localization performance. An effect of SNR can be appreciated for both FBpc and Lscat in both adults and children. Increase in SNR increases FBpc and reduces Lscat, but no effect of age can be observed. This is consistent with a regression analysis; age as independent variable and both FBpc and Lscat as dependent variables did not show any systematic age effect within children (FBpc_{BBN}: $\beta = 0.05$, $t[18] = 0.51$, $p = 0.619$; FBpc_{SB}: $\beta = 0.06$, $t[18] = 0.58$, $p = 0.570$; Lscat_{BBN}: $\beta = -0.01$, $t[18] = -0.04$, $p = 0.973$; Lscat_{SB}: $\beta = -0.12$, $t[18] = 0.40$, $p = 0.694$), therefore the child group was collapsed across age for further analyses.

Individual FBpc and Lscat values for every participant and corresponding group means are plotted in Figure 4-6 as a function of SNR. As evidenced in the figure, mean localization performance improves with increasing SNR for both adults and children.

FBpc performance is better in SB compared to BBN for both adults and children, as would be expected based on the low-pass characteristic of SB. However, children's FBpc values appear slightly below adult levels for SB, despite similar performance in quiet and in BBN. Mean FBpc ranged from 79±4.4% at -12 dB SNR to 92±3.4% at 0 dB SNR for BBN in adults.

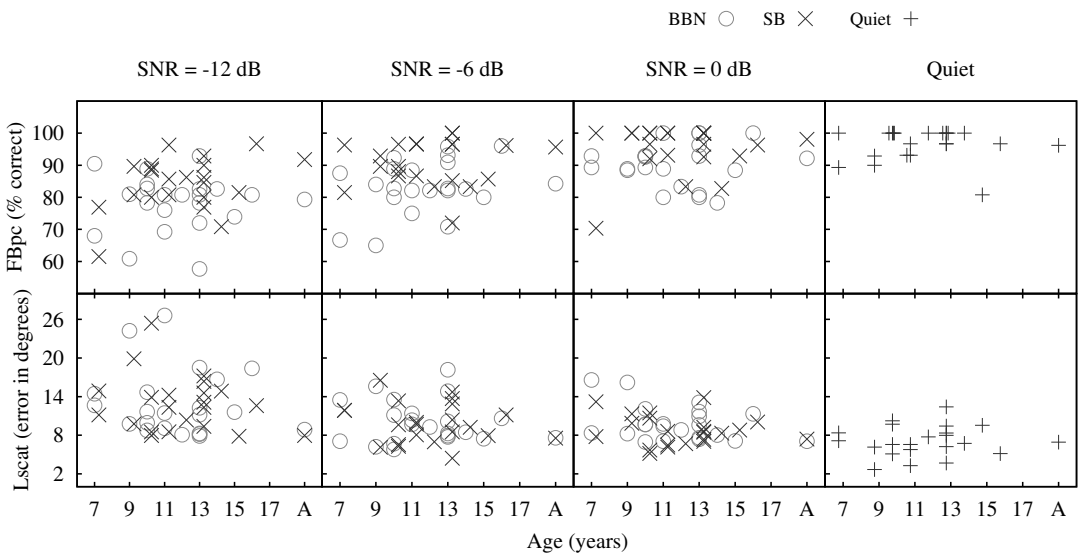

Figure 4-5: Localization data plotted as a function of age with FBpc on the top row and Lscat on the bottom row. This plot indicates that there is no trend in either measure across age. In the top row, higher scores are better, in the bottom row, lower scores are better. Note that the adult data (age A) are the means for all 21 participants, and that jitter (±0.25 years) has been added to children's ages for better visualization.

The slope of this improvement in FBpc across SNR in adults equated to 1.05%/dB. Similar improvement for BBN was also seen in children; mean FBpc values were 78±3.8% at -12 dB SNR for BBN to 90±2.9% at 0 dB SNR. The improvement slope in children was very similar to adults, with a value of 1%/dB (Figure 4-6A). However, for SB, adults performed at 92±2.8% even at -12 dB SNR, and this improved to 98±0.9% at 0 dB SNR, which equated to a shallow slope of 0.52%/dB. Children also showed improvement in FBpc in SB compared to BBN; FBpc varied from 84±3.6%

at -12 dB SNR to 95±3.3% at 0 dB SNR. However, children's SNR slope for SB was numerically steeper at 0.91%/dB (Figure 4-6B).

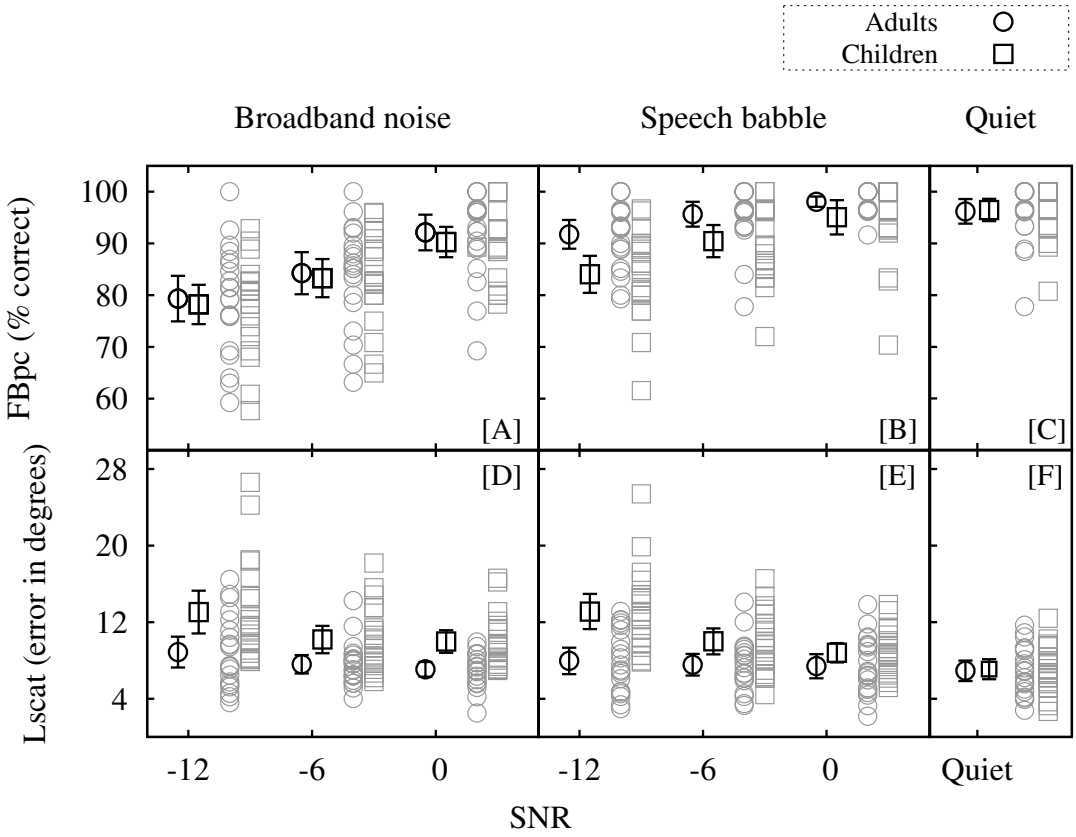

Figure 4-6: Localization data plotted as a function of SNR, with FBpc on the top row and Lscat on the bottom row. Labels above each column of panels describe the masker conditions. Plotted data are mean (black symbols) and raw values (grey symbols) for adults (circles) and children (boxes) as a function of SNR. Error bars around the means represent 95% confidence intervals. Larger FBpc in the top panel and smaller Lscat in the bottom panel indicate better localization.

In contrast to FBpc, means of Lscat are separated markedly different between adults and children. Children appear to benefit from increasing SNR, whereas adults appear to perform equally well, and consistently better, than children at all SNRs. Also, unlike FBpc, Lscat is similar for both maskers. In children, Lscat improved, i.e., decreased from 13 ± 2.2° at -12 dB SNR to 9.9±1.2° at 0 dB SNR for BBN and

from 13±1.8° at -12 dB SNR to 8.8±1° at 0 dB SNR for SB. However, such an SNR effect was not observable in adults. Lscat at -12 dB SNR for BBN was 8.9±1.6° and 7.1±0.8° at 0 dB SNR in BBN and 7.9±1.4° at -12 dB SNR to 7.4±1.3° at 0 dB SNR for SB.

As seen in Figures 4-6C and 4-6F, adults and children performed at equal levels in quiet for both FBpc and Lscat, respectively. Mean adult group FBpc was 96.20 ±2.36% and Lscat was 6.92±1.06%, and mean child group FBpc was 96.47±2.17% and Lscat was 7.08±1.04%. Independent-sample t-tests performed to test for group differences in the quiet condition reflect this for both FBpc ($t[40] = 0.03$, $p = 0.97$) and Lscat ($t[40] = 0.22$, $p = 0.83$). Localization ability in quiet obtained in the present study is thus consistent with previous studies that show adult-like localization in five-year-old children (Litovsky, 1997; Van Deun et al., 2009).

Further, to ascertain main effects of SNR, masker and group, and their interactions, a split-plot (mixed design) ANOVA (SP-ANOVA) with localization measures (FBpc and Lscat) as dependent variable, and masker, SNR, and group (adults versus children) as independent variables was performed. Results were interpreted with Greenhouse-Geisser corrections if the assumption of sphericity was violated. Post-hoc tests were interpreted with false discovery rate (FDR: Benjamini & Hochberg, 1995) corrections ($\alpha = 0.05$) for performing multiple comparisons. Results indicate a significant main effect of masker for FBpc ($F[1,40] = 43.65$, $p<0.001$, ${\eta^2}_{Partial} = 0.52$), but not for Lscat ($F[1,40] = 1.01$, $p = 0.32$, ${\eta^2}_{Partial} = 0.03$). This result suggests that when data were pooled across SNRs and groups, there was a significant difference in FBpc between the two maskers for FBpc. There was also a significant main effect of SNR for both FBpc ($F[2,80] = 101.30$, $p<0.001$, ${\eta^2}_{Partial} = 0.72$) and Lscat ($F[2,80]=23.44$, $p<0.001$, ${\eta^2}_{Partial} = 0.37$). This suggests that when data were

pooled across maskers and groups, localization performance improved as a function SNR, as expected, and as evidenced in Figures 4-6A, B, D and E.

The apparent difference in FBpc across SNRs for the two maskers caused a significant interaction between masker and SNR for FBpc ($F[2,80] = 3.67$, $p = 0.03$, $\eta^2_{Partial} = 0.08$). Post-hoc comparisons show significantly lower FBpc in the BBN condition compared to SB at all SNRs ($SNR_{\{-12\ dB\}}$: Mean difference [MD] = -9.13%, $CI_{95\%} = \pm 3.60\%$; $t[41]$ = -4.97, $p<0.001$; $SNR_{\{-6\ dB\}}$: MD = -9.28%, $CI_{95\%} = \pm 3.13\%$, $t[41]$ = -5.93, $p<0.001$; $SNR_{\{0\ dB\}}$: MD = -5.36%, $CI_{95\%} = \pm 2.41\%$, $t[41]$ = -4.54, $p<0.001$). This result suggests that BBN causes significantly larger disruption of F/B localization than SB. Note that this result is obtained when data were collapsed across groups considering no group interactions were found.

Contrary to FBpc, the qualitative differences between adults and children in Lscat (Figures 6D and E) were consistent with a significant group interaction (group X SNR) ($F[2,80] = 6.63$, $p = 0.02$, $\eta^2_{Partial} = 0.14$). Considering no 3-way interaction (Group X SNR X Masker) was found ($F[2,80] = 1.43$, $p = 0.25$, $\eta^2_{Partial} = 0.04$), data were collapsed across maskers for post-hoc analysis.

Results of this post-hoc analysis show significantly higher Lscat in children at all SNRs compared to adults ($SNR_{\{-12\ dB\}}$:MD = 4.67°, $CI_{95\%} = \pm 2.21°$, $t[40]$ = 4.27, $p<0.001$; $SNR_{\{-6\ dB\}}$: MD = 2.51°, $CI_{95\%} = \pm 1.60°$, $t[40] = 2.50$, $p = 0.003$; $SNR_{\{0\ dB\}}$: MD = 2.16°, $CI_{95\%} = \pm 1.26°$, $t[40] = 3.46$, $p = 0.001$). Results of Lscat suggest that childrens' localization-in-noise is more variable than adults, consistent with Litovsky and Godar (2010). Results of Lscat also suggest that adults' lateral localization is robust on a trial-by-trial basis, even in the poorest SNR, consistent with Good and Gilkey (1996).

Despite qualitative difference in FBpc between adult and children (as seen in Figure 4-6B) for the SB masker, considering there were no group interactions in the omnibus ANOVA, further group specific post-hocs could not be conducted. Therefore, t-tests for slopes of both measures (FBpc and Lscat) were conducted (and interpreted with FDR corrections) to further evaluate if the aforementioned numeric differences were significant. Results showed that improvement in localization as a function of SNR, i.e., slope, differs significantly between adults and children for both FBpc (t[40] = 2.43, p = 0.02) and Lscat (t[40] = -3.39, p = 0.002) in SB masker, but not for BBN; FBpc (t[40] = -0.28, p = 0.78) and Lscat (t[40] = -1.07, p = 0.29). This is consistent with Figures 4-6A, B, D and E, and suggests that adults localize better than children in the F/B dimension in SB, but not in BBN.

4.3.2 Part II: MOC inhibition of CEOAEs

To investigate group differences between MOC inhibition of CEOAEs evoked by MOC elicitors of different lateralities (ipsi, contra and binaural), a one-way RM-ANOVA, with CEOAE inhibition as dependent variable and group as independent variable, was conducted. Results indicate no interaction between MOC elicitor lateralities and group (F[2,66] = 1.76, p = 0.179, $\eta^2_{Partial}$ = 0.05), suggesting that MOC-mediated CEOAE inhibition across different MOC elicitor lateralities was similar across the two groups. This result is not surprising as previous studies have indicated that MOC (contralateral) inhibition of OAEs is mature at birth (Abdala et al., 2013). There was however a main effect of MOC elicitor laterality (F[2,66] = 94.51, p<0.001, $\eta^2_{Partial}$ = 0.74).

Post-hoc tests with pooled group data show that the binaural MOC elicitor evoked significantly larger inhibition of CEOAEs than either ipsilateral (MD = 18.67%, $CI_{95\%}$ = ±4.25%, t[34] = 10.72, p<0.001) or contralateral elicitors (MD = 19.83%, $CI_{95\%}$ = ±3.49%, t[34] = 14.45, p<0.001), as evident in Figure 4-7A.

To study binaural interaction in the elicitation of MOC inhibition, the mBIC was calculated based on the following equation;

$$mBIC = (ipsi + contra)\ inhibition - binaural\ inhibition \tag{4.1}$$

As evidenced in Figure 4-7B, the mBIC is predominantly negative in both groups, indicating that binaural MOC-mediated inhibition of CEOAEs was larger than the sum of the two monaural (ipsilateral + contralateral) inhibitions (MD = 4.47%, $CI_{95\%}$ = ±2.13%, $t[34] = 4.07$, $p<0.001$)

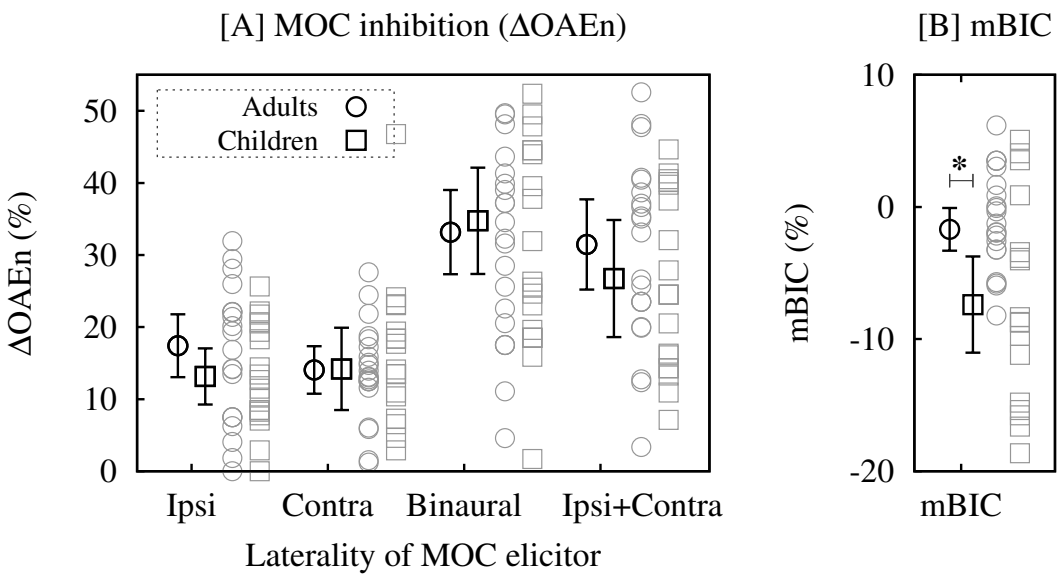

Figure 4-7: MOC inhibition of CEOAE and MOC binaural interaction component (mBIC). Black symbols are the mean MOC inhibition of CEOAE (%) in each of the different MOC elicitor lateralities plotted on the x-axis. Corresponding grey symbols are individual inhibition data. Circles represent adults and boxes represent children. The asterisk in the mBIC panel (B) indicates a significant mean difference in a independent sample *t*-test between adults and children. The Y-axis in panel A is normalized mean inhibition (%), and in panel B it is mBIC (%).

Negative mBIC suggests binaural facilitation, while positive mBIC suggest binaural inhibition$_A$[2] at the level of the brainstem. An independent-sample t-test showed that mBIC was significantly more negative (t[22.13] = -2.80, p = 0.01 [Note that degrees of freedom from this t-test is corrected for unequal group variances.]) in children (Mean = -7.39%; $CI_{95\%}$ = ±3.64%) compared to adults (Mean = -1.70%; $CI_{95\%}$ = ±1.61%). This results suggests that the child group had significantly negative mBIC, indicating a predominance of binaural facilitation.

4.3.3 Binaural MOC function and localization-in-noise

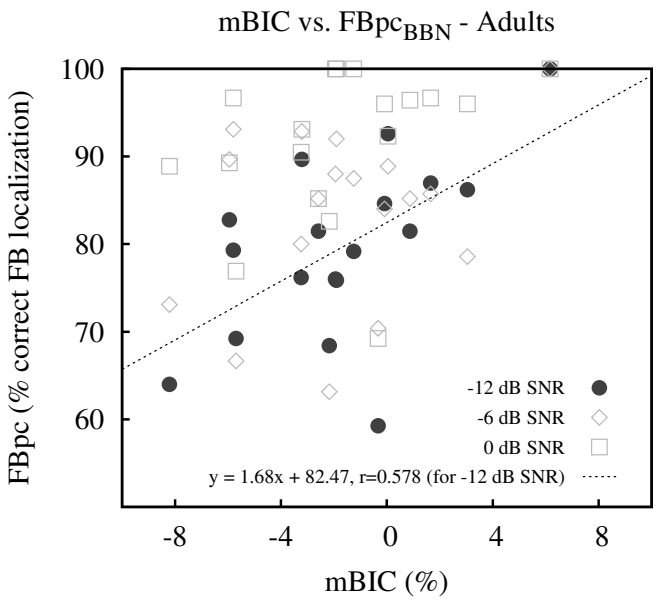

Figure 4-8: Scatter plot of FBpc$_{BBN}$ in adults as a function of mBIC showing a significant correlation at -12 dB SNR (filled circles). The significant relationship is shown as a linear-fit line (dashed), and its corresponding equation is provided in the key. No correlation was found at higher SNRs in adults (diamonds and squares), or at any SNR in children.

[2]In order to avoid confusion between binaural neural *inhibition* at the brainstem level and MOC *inhibition* of CEOAEs, we will refer to binaural neural inhibition as inhibition$_A$ (subscript 'A' refers to afferent pathway). Note that these terms are descriptive (McPherson & Starr, 1993).

Correlation analyses were done to elucidate the relationship between MOC-mediated inhibition of CEOAEs and localization measures across listeners for the two maskers and SNRs separately. FBpc in BBN (FBpc_{BBN}) for adults for all SNRs is plotted as a function of mBIC in Figure 4-8. As seen in the figure, it is only FBpc_{BBN} (filled circles) at the lowest SNR (-12 dB) in adults that shows a significant correlation. No other SNRs or maskers correlated with mBIC in adults. mBIC significantly predicted $\text{FBpc}_{BBN(-12 \text{ dB SNR})}$, b=1.67, $t[16] = 2.83$, $p = 0.01$. mBIC also explains a significant proportion of the variance in $\text{FBpc}_{BBN(-12 \text{ dB SNR})}$, $R^2 = 0.33$, ($F[1,16] = 8.04$, $p = 0.01$). However, following FDR corrections for performing multiple correlations, this significance was lost. No significant correlations were found for any FBpc SNR and mBIC in children. All correlation coefficients for FBpc are tabulated in Table 4-1.

	Correlation coefficients (r)			
SNR	**Adults**		**Children**	
	BBN	**SB**	**BBN**	**SB**
-12	0.578	0.032	0.108	-0.238
-6	0.303	0.043	0.111	-0.172
0	0.330	-0.139	-0.375	-0.073

Table 4-1: Correlation coefficients (r) obtained for comparisons between mBIC and FBpc across groups, SNRs and maskers.

4.4 Discussion

4.4.1 Part I: Localization

F/B localization

The first goal of this study was to investigate children's F/B localization in comparison to adults in two different types of maskers: BBN and SB. FBpc results in

quiet provide evidence that children are able to grossly distinguish between a speech sound ('baseball') arriving from the front and rear as accurately as adults. This result extends the existing literature on children's localization ability in quiet in the front hemi-field (Grieco-Calub & Litovsky, 2010; Litovsky, 1997; Van Deun et al., 2009). These investigators showed that localization in quiet is adult-like at 5 years of age. Further, BBN appears to have similar effects on gross F/B localization in both adults and children. However, visual examination of FBpc means in Figure 6B and the significant difference between adults and children for FBpc slopes in SB collectively suggest that children's gross F/B localization is disrupted more by SB compared to the adults. Considering that no effect of age in F/B localization (FBpc) was observed in the present study, it can be suggested that F/B localization in BBN, but not in SB, is also is adult-like by 7 years of age.

Improvement in FBpc as a function of SNR is also similar in adults and children, but thresholds from the present study appear better than similar previous reports in adults (Abouchacra et al., 1998; Good & Gilkey, 1996). Abouchacra et al. (1998) reported that their adult participants obtained 85% FBpc at around 10 dB SNR. In the current study, both children and adults reached 85% FBpc$_{BBN}$ at around -6 dB SNR in BBN. Good and Gilkey (1996) reported that among lateral, F/B and up/down (U/D) dimensions, the F/B was most affected by noise. Their participants on average scored 65% FBpc at around -2 dB SNR. The difference between the results of the current study and those of Abouchacra et al. (1998) and Good and Gilkey (1996) could arise due to several methodological factors. Firstly, differences in the method of calculation of localization errors may have contributed considerably to the observed differences in localization ability. In the present study, only the gross FB error was obtained, and no RMS azimuth errors were calculated, since they do not provide accurate information on the type of localization error. Abouchacra et al.

(1998) did not calculate a direct FBpc because they did not include a front loudspeaker in their experiment (0°), therefore any response in the midline was biased towards the rear (180°). To avoid this, we only compared their 'mid-front' and 'mid-back' (their Figures 2A and 2C, respectively) results with our own. Good and Gilkey (1996) on the other had used a three-pole coordinate system that converted lateral, F/B and U/D localization errors to a single plane. Nevertheless, Good and Gilkey (1996) ultimately calculated RMS error as one of their measures to quantify FBpc. Considering both studies have used RMS error, which describes the degree of error in greater detail compared to FBpc in the present study, an apparent difference in overall performance can be expected. Thus, a direct comparison between the results of the present study and previous studies may not be applicable.

Better FBpc performance in SB compared to BBN was expected based on spectral and temporal differences between maskers. First, SB does not mask high frequencies (>4 kHz) as effectively as BBN, due to the low-pass nature of the speech spectrum. Considering that high-frequency information is critical for F/B localization (Langendijk & Bronkhorst, 2002; Roffler & Butler, 1968), better F/B localization can be expected in SB than in BBN. Second, due to the presence of amplitude fluctuations in speech, SB may promote 'dip-listening' (Cooke, 2006; Festen & Plomp, 1990; Nelson, Jin, Carney, & Nelson, 2003) by allowing listeners to exploit momentary improvements in SNR to localize better (Kopco et al., 2010; Yost & Brown, 2013). Although not significant in the omnibus ANOVA, there was a significant difference in rate of improvement in FBpc across SNR (slope) between adults and children. Adults performed better than children at worse SNRs, therefore their improvement as a function of SNR was restricted. However, children caught up to adult levels at 0 dB SNR, despite inferior performance at lower SNRs. This difference in performance across SNRs caused a difference in their FBpc slopes. This result is interesting because chil-

dren performed at adult levels in both the quiet and BBN masker conditions. The difference in performance cannot be attributed to spectral differences between BBN and SB, because as evidenced in BBN, energetic masking is similar between adults and children. Two reasons for the difference in F/B localization in SB between adults and children can be envisaged. First, although localization in quiet is mature at five years of age, and gross FBpc in BBN by 7 years of age, differences in maturational trajectories of other auditory processes such as temporal resolution (Hall & Grose, 1994; Hartley, Wright, Hogan, & Moore, 2000; Hill, Hartley, Glasberg, Moore, & Moore, 2004; Wightman, Allen, Dolan, Kistler, & Jamieson, 1989) may limit childrens' ability to extract the target embedded in SB (Garadat & Litovsky, 2007). Due to an inadequacy in temporal resolution, perhaps children are unable to extract target information as well as adults using dip-listening (Garadat & Litovsky, 2007). Although it can be argued that the number of temporal dips in a multi-talker babble is limited compared to a single-talker masker, it would always be more than with BBN. For this reason, the possibility that adults were able to exploit subtle temporal dips in SB to localize better than children cannot be ruled out.

Secondly, the presence of linguistic content, although unintelligible, in the SB masker could have caused larger informational masking in children, affecting their overall performance. Informational masking is a phenomena in which elevation of thresholds due to a masker cannot be explained by energetic masking alone (Oh, Wightman, & Lutfi, 2001). Indeed SB is known to cause informational masking (Brungart, Simpson, Ericson, & Scott, 2001), and children are known to be more prone to informational masking (Hall, Buss, & Grose, 2005; Oh et al., 2001; Wightman, Callahan, Lutfi, Kistler, & Oh, 2003), and distraction (Allen & Wightman, 1994; Lutfi, Kistler, Oh, Wightman, & Callahan, 2003). Increased informational masking due to SB may also relate to its higher temporal uncertainty compared to

BBN (Lutfi, 1990). Considering that children are able to grossly localize sounds in the F/B dimension as well as adults in both quiet and BBN, the difference in FBpc between adults and children in SB suggests that there is more than energetic masking at play for SB. This is because both BBN and SB energetically mask the target, although with different strengths. If only energetic masking were at play, one would expect equal performance in SB between adults and children, mirroring the BBN results, which does not appear to be the case here. Therefore, it can be proposed that a combination of developmental factors, particularly pertaining to temporal resolution, and potentially higher informational masking, may have led to lower FBpc in children in SB compared to adults.

Lateral angle localization

Results of Lscat-in-noise show significant group effects in both raw values and slopes; the accuracy of localization-in-noise in children is significantly lower than in adults. This suggests that although children are able to grossly differentiate sounds arriving from the front and back, their responses in noise are not as consistent as adults. Developmental studies in binaural hearing show that peripheral encoding of binaural signals may be mature at birth but that central neural processes may continue to develop until at least six years of age when measured using binaural masking level difference (BMLD; Hall & Grose, 1990; Moore, Cowan, Riley, Edmondson-Jones, & Ferguson, 2011). Temporal resolution measured using gap detection is also adult-like at five years of age (Trehub, Schneider, & Henderson, 1995), although when measured using backward masking, it continues to develop at least until 10 years of age (Hartley et al., 2000), which shows the influence of noise in children's hearing. The typically obtained measure of localization, minimum audible angle (MAA) thresholds, are adult-like at 5 years of age (Litovsky, 1997; Van Deun et al., 2009), in addition to ITD sensitivity, which also reaches 90% of adult values by 5 years (Ashmead et

al., 1991). Accordingly, Litovsky (1997) suggested that localization in quiet may not entirely depend on temporal resolution. It thus appears that children in the age range tested in the present study would be expected to have a mature binaural system that should allow them to localize as precisely as adults. Thus, maturational trajectories obtained in quiet for temporal resolution, ITD sensitivity, and binaural hearing may not explain the observed difference in localization accuracy between adults and children, as they are adult-like in 5 year olds. In line with this evidence, lack of difference in Lscat-in-quiet between the two groups does suggest that the neural circuitry and motor skills required to respond as accurately as adults are present in children, at least in quiet. However, children's performance in noise suffered significantly more than adults. This is also evident in their FBpc scores in SB.

One reason for this inconsistency could be related to overall lower processing efficiency of children in auditory tasks arising from higher "internal noise", thus requiring higher SNR than adults (Hill et al., 2004). Two different kinds of internal noise have been described by Oxenham and Buus (2000). The first type, dubbed sensation noise, arises due to the signal encoding process. The second type, dubbed central noise, is stimulus independent and is thought to arise due to central auditory and memory related processes in the auditory system (Oxenham & Buus, 2000). It is possible that children use more central resources to combat the effects of acoustic noise. This is perhaps due to inexperience, which potentially results in higher central noise (Werner & Bargones, 1991), and poorer localization accuracy. However, measures of internal noise assume that a listener is attentive to the target (Amitay, Zhang, Jones, & Moore, 2013) and children are known to be less attentive than adults (Allen & Wightman, 1994; Leibold & Bonino, 2009; Litovsky & Godar, 2010; Lutfi et al., 2003; Newman, 2009; Oh et al., 2001). Monitoring more 'auditory filters' than required has been posited to be one of the reasons for distraction in children

(Allen & Wightman, 1994; Lutfi et al., 2003). By monitoring more than the required auditory filters, children may place less weight on the target filter compared to adults. This may affect signal integrity, and thus internal SNR (Faisal, Selen, & Wolpert, 2008), which in turn may increase the work load of higher auditory centers, resulting in reduced overall efficiency (Hill et al., 2004). However, training related improvement in reduction of internal noise has recently been reported (Jones, Moore, Amitay, & Shub, 2013). This is thought to be achieved by promoting higher weights for the target stimulus during the decision making process, which occurs as a result of learning. Perhaps due to increased experience and learning, adults are better able to monitor the correct filters, which may reduce their cognitive work load. In addition, similar to FBpc SNR slope, the slope of Lscat (as a function of SNR) was only significantly different between the groups for SB. Despite significant differences in Lscat in BBN, group slopes were not significantly different. This again suggests that children are more prone to informational masking, which affects their localization in a multi-talker babble. It can thus be suggested that an interplay of variables such as distraction, informational masking and higher central noise, arising from reduced processing efficiency, could have led to childrens' poor localization accuracy in noise.

4.4.2 Part II: Binaural MOC function

In line with previous studies on the maturation of MOC function (Abdala, Ma, & Sininger, 1999; Abdala et al., 2013; Chabert et al., 2006; Ryan & Piron, 1994), data from the present study shows that contralateral MOC function is mature in the age group tested. As with contralateral MOC function, both ipsilateral and binaural MOC function in children are indistinguishable from adults when individual MOC elicitor lateralities are considered. Previous binaural MOC studies have shown that contralateral and ipsilateral MOC inhibition of OAEs are the same (Berlin et al., 1995; Lilaonitkul & Guinan, 2009) and that binaural MOC activation causes signif-

icantly larger inhibition of OAEs compared to monaural activation. The findings are consistent with the findings of the present study.

Few studies have investigated binaural MOC inhibition of OAEs (Backus & Guinan, 2006; Berlin et al., 1995; Lilaonitkul & Guinan, 2009; Philibert, Veuillet, & Collet, 1998), and none of them have explored the concept of binaural interaction. Backus and Guinan (2006) briefly mentioned the existence of interaction at the level of the MOC. Two of their participants exhibited binaural facilitation, while one of them exhibited inhibition$_A$. The results obtained here are thus novel for the MOC realm. But what does mBIC signify, and how is it related to localization? To answer this, parallels to the binaural interaction component (eBIC[3]) described in the auditory evoked potential literature can be considered.

The concept of the binaural interaction component has been investigated widely in the auditory evoked potentials literature, and it is thought to reflect binaural processing (Dobie & Norton, 1980; Gardi & Berlin, 1981; McPherson & Starr, 1993). In the evoked potential literature, the binaural response is typically smaller than the sum of monaural responses (positive eBIC) (McPherson & Starr, 1993) or no difference between the two is observed (Dobie & Norton, 1980; Gopal & Pierel, 1999). In the present study, the mBIC was, on average, negative for both groups. Anatomically speaking, it has been found that the more rostral the generation site, the larger the binaural response, i.e., larger eBIC (McPherson & Starr, 1993; Wada & Starr, 1989). If the efferents are governed by the same gradient in binaural inhibition that applies to eBIC, the position of MOC neurons (Liberman, 1988; Warr, 1992) towards the caudal end of this gradient would predict minimal inhibition or

[3]To avoid confusion between the two types of binaural interaction components discussed in this study (derived from MOC or evoked potential measurements), the binaural interaction component described in the evoked potential literature will be referred to as eBIC throughout this chapter.

even facilitation. Another explanation for the differences between mBIC and eBIC could be that mBIC is an efferent response, while eBIC is an afferent response.

Indirect corticofugal projections that traverse via collicular nuclei (Huffman & Henson, 1990), and direct cortico-olivary projections (Coomes & Schofield, 2004; Mulders & Robertson, 2000) from cortex to the MOC have been identified. These projections are involved in adjusting the gain of sensory input to higher centers, forming a feedback loop (Robinson & McAlpine, 2009). A predominantly excitatory-facilitatory role has been suggested for corticofugal connections to various brainstem nuclei (Feliciano & Potashner, 1995; Lamas, Alvarado, Carro, & Merchan, 2013). Further, cortical connections to the brainstem terminate bilaterally, although they are stronger on the ipsilateral side (Coomes & Schofield, 2004), therefore excitation of binaural MOC can be expected. This corticofugal excitation may in part augment the MOC's response for binaural sound stimulation. The afferent pathway, in contrast, does not receive such a binaural augmentation, which may lead to a larger eBIC as evidenced in evoked potentials. Should such an augmentation of binaural response exist in the MOC, it could counteract inhibition$_A$ witnessed in the afferent pathway. In addition, Liberman and Brown (1986) showed that MOC neurons exhibit binaural facilitation, i.e., an increase in spike rate when a second stimulus is added to the contralateral ear. Considering most MOC neurons respond to binaural stimulation, in addition to those that are dedicated binaural units, it is also possible that binaural facilitation is predominant in the MOC (Liberman & Brown, 1986). Brown, Kujawa, and Duca (1998) also studied the binaural properties of the MOC and suggested that most MOC neurons are facilitated by binaural stimulation, which could lead to a negative mBIC. In contrast, afferent responses from the medial superior olive (MSO) and lateral superior olive (LSO) show inhibition to binaural stimulation (Covey, Vater, & Casseday, 1991; Grothe & Sanes, 1993). In essence, the mBIC indicates the

interaction of binaural afferent inputs and corticofugal influence at the MOC. Since all modes of MOC activation are included in mBIC, it may portray a complete picture of MOC activity, compared to contralateral, ipsilateral and binaural MOC inhibition of CEOAEs alone.

The present study considered the difference in mBIC between groups, which suggest differential MOC function between adults and children. Children show significantly more negative mBIC, suggesting that the MOC response is significantly larger when activated binaurally (with respect to ipsi + contra monaural inputs). This result is unexpected, considering there are no maturational factors at play (Abdala et al., 2013). The eBIC too, although not consistently observed in both ABRs and MLRs in neonates (Cone-Wesson, Ma, & Fowler, 1997; McPherson, Tures, & Starr, 1989), is consistently present in children at least at seven years of age (Gopal & Pierel, 1999). The additional MEMR tests conducted in this study provide confidence that larger binaural OAE inhibition is due to MOC activation, and not due to the MEMR. Therefore, a straightforward explanation for the observed group difference in mBIC based on the current literature is unavailable. One speculation could be based on subtle asymmetries in MOC inhibition of CEOAEs across elicitor lateralties. Although not significant, the subtle difference between contralateral and ipsilateral inhibition seen in adults is not present in children (Figure 4-7A). While studies have investigated asymmetries between left and right ears (e.g., McFadden, 1993), there are no data on ipsilateral versus contralateral MOC inhibition of CEOAEs across different age groups. Perhaps the mBIC is sensitive to such subtle asymmetries, and therefore requires further close examination. However, an effect of age was not observed within children in the current data.

4.4.3 Binaural MOC function and localization-in-noise

Only a few studies have investigated the relationship between efferent functioning and localization (Andéol et al., 2011; Darrow et al., 2006; Irving, Moore, Liberman, & Sumner, 2011). These studies unequivocally show that that efferents facilitate localization. The strength of the MOC is strongly correlated with median plane localization (Andéol et al., 2011), which is thought to be due to MOC unmasking of spectral cues. However, Andéol et al. (2011) only studied the relationship between localization-in-noise and contralaterally evoked MOC, i.e., uncrossed MOC fibers. The present study sought to extend this further by evoking the MOC binaurally, thereby activating both the crossed and uncrossed MOC reflex. The mBIC provides an objective measure of binaural interaction of the MOC. However, unlike in Andéol et al. (2011), correlation between F/B localization and mBIC was not significant at any SNRs. Although, a significance was found for the poorest SNR (-12 dB) in adults, this was lost due to FDR corrections.

First, the difference in results between the two studies can be explained based on the localization task. Andéol et al. (2011) used targets that included variation in the U/D dimension. The current study however, involved only the F/B and L/R dimensions. It is possible that the MOC is more critical for unmasking the spectral cues for U/D localization than those for F/B localization. Thus, the inclusion of the U/D dimension in Andéol et al. (2011) could explain their larger correlations found between localization-in-noise and MOC inhibition of CEOAEs, compared to the present study.

Secondly, the presence of a trend only at the worst SNR may be explained by a lack of spread in the data. Many adults were performing at 75% or higher at better SNRs (>-12 dB), and there appears to be less spread in the data for -6 and 0 dB SNRs. This lack of correlation may thus be dependent on task difficulty rather than

a lack of relationship between mBIC and FBpc. The same would apply for Lscat for adults. However, considering that children performed at the same level as adults in $FBpc_{BBN}$, the task-difficulty hypothesis may not apply to children. One potential explanation for the presence of correlation in adults and its absence in children could be based on the sensitivity of the MOC to attention. Previous studies have shown that the MOC influence on the cochlea can be enhanced through focused attention (Garinis et al., 2011; Maison et al., 2001) that may even reduce physiological noise in the ear-canal (Walsh, Pasanen, & McFadden, 2014). Poor SNR can be thought to demand increased attention to perform the same task effectively. This increased attention may consequently enhance corticofugal influence on the cochlea via the MOC (Smith, Aouad, & Keil, 2012; Srinivasan, Keil, Stratis, Woodruff Carr, & Smith, 2012). It is possible that adults attended to the target more in the poorest SNR conditions relative to better SNR conditions. Perhaps, this increased attention caused a larger binaural MOC activation, resulting in better correlation between mBIC and F/B localization-in-noise in adults at -12 dB SNR.

On the other hand, the poorer localization accuracy and potentially larger informational masking evidenced in children may suggest that children did not attend to the stimulus as well as adults, leading to lower corticofugal influence on the periphery. Collectively, these findings suggest that the MOC may be involved in localization-in-noise, and may play a larger role in poorer SNRs and particularly in unmasking spectral contrasts. Therefore, MOC activation may be more beneficial for U/D localization compared to azimuthal localization, due to its reliance on spectral cues (Andéol et al., 2011). Considering task dependent attention was not systematically studied or controlled in the present experiment, the relationship between attention-augmented improvement in localization-in-noise and its relationship to MOC function can neither be confirmed nor rejected. However, these results provide impetus for fur-

ther studies involving U/D localization, and for including control of attention to shed more light on the relationship between localization-in-noise and binaural MOC function.

The direction of correlation between $\text{FBpc}_{BBN(-12\ dB)}$ and mBIC (Figure 4-8) suggest that binaural inhibition_A may be beneficial for localization-in-noise. However, from current physiological evidence, it appears that binaural inputs are largely facilitated in the MOC. Although both facilitation and inhibition_A are seen in both groups, their respective roles and the reasons for such large differences across samples is elusive. Further physiological studies are required to better understand binaural interaction in the MOC and its implications for hearing.

4.5 Conclusion

Two experiments were conducted to investigate (1) the localization-in-noise ability of children, and (2) the relationship between binaural MOC function and localization-in-noise. Results indicate that while children are able to grossly differentiate sounds arriving in the F/B dimension, their localization accuracy is not on par with adults. Differences in binaural MOC function (mBIC) between adults and children were also found. For reasons which are not clear, adult localization-in-noise correlates better with binaural MOC function, perhaps due to augmentation of MOC by focused attention. Further studies are warranted to better understand the observed difference in mBIC between adults and children, and the relationships between binaural MOC function and median plane localization.

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Chapter 5

Cochlear Tuning and Medial Olivocochlear Functioning in Children with Suspected Auditory Processing Disorder

5.1 Introduction

"Auditory Processing Disorder (APD) refers to difficulties in the perceptual processing of auditory information in the central nervous system and the neurobiological activity that underlies the processing" (American Academy of Audiology [AAA], 2010). Difficulty hearing speech-in-noise despite normal hearing thresholds is the hallmark of APD (Chermak, Hall, & Musiek, 1999). APD is a heterogeneous disorder involving a breakdown of various aspects of auditory processing, resulting in complaints and symptoms that vary remarkably across the population (D. R. Moore, 2006). Problems at various levels of the auditory neural system in both the afferent (bottom-up) pathway and in the higher level processing that fine-tunes afferent pathways via efferent connections (top-down) have been reported in APD (British Society of Audiology [BSA], 2011). For example, studies have shown atypical auditory encoding at the brainstem (Allen & Allan, 2014; Anderson, Skoe, Chandrasekaran, Zecker, & Kraus, 2010; Cunningham, Nicol, Zecker, Bradlow, & Kraus, 2001; Gopal & Pierel, 1999;

Song, Skoe, Banai, & Kraus, 2011; Wible, Nicol, & Kraus, 2002), midbrain (Hall & Johston, 2007; Musiek, Charette, Kelly, Lee, & Musiek, 1999; Purdy, Kelly, & Davies, 2002), and the cortex (Abrams, Nicol, Zecker, & Kraus, 2009; McArthur, Atkinson, & Ellis, 2009) in children with listening problems. However, cochlear processing remains unexamined in these children.

Peripheral auditory mechanisms are not typically included in the diagnosis of APD, rather, they are only screened for the presence of an overt hearing loss. However, the cochlea performs substantial signal processing that is crucial for speech perception. Cochlear tuning is directly related to frequency selectivity and temporal processing ability (B. C. J. Moore, 1993; D. R. Moore, 2007), and therefore is important for good speech discrimination, especially in noise (Dorman, Loizou, Fitzke, & Tu, 1998; B. C. J. Moore, 2003b). Impaired cochlear tuning increases masking and reduces suppression, which can in turn reduce contrasts between speech sounds and affect speech perception (Festen & Plomp, 1983; B. C. J. Moore, 1985). Although cochlear tuning impairments are typically seen in individuals with cochlear hearing loss, Badri, Siegel, and Wright (2011) reported broader tuning in normal hearing adults who complained of poor speech discrimination in noise. Patterson, Nimmo-Smith, Weber, and Milroy (1982) previously showed that cochlear tuning deteriorated with age, despite clinically normal hearing sensitivity. This suggests that conventional audiograms and speech tests in quiet do not capture subtle deficits in cochlear functioning that can impact speech perception in noise, which is typical of APD. Although speech impairments are most often mentioned for those with poor tuning, unusually sharp tuning impacts temporal aspects of speech perception (Shailer & Moore, 1983; Zheng et al., 2011). Hence, there appears to be a range of optimal cochlear filter widths. To better understand cochlear processing in children with listening problems, an objective physiological measure of cochlear tuning, stimulus frequency otoacoustic

emission (SFOAE) group delay (Shera, Guinan, & Oxenham, 2002; Shera & Zweig, 1993) was used in the present study to investigate cochlear tuning.

Cochlear processing, including tuning, does not happen in isolation, it is influenced by corticofugal connections (top-down) via the medial olivocochlear system (MOC; Khalfa et al., 2001; Winer, 2006; Xiao & Suga, 2002). MOC axons innervate outer hair cells (OHCs) directly and due to their cholinergic nature, reduce OHC electromotility and thus cochlear amplification (Guinan & Gifford, 1988). This inhibitory action reduces otoacoustic emission (OAE) level (review: Guinan, 2006) and alters cochlear tuning (Francis & Guinan, 2010). Such subtle changes have been hypothesized to affect pitch perception and localization abilities (Francis & Guinan, 2010). MOC inhibition of OAEs is of particular interest in the APD population because it aids in unmasking signals from noise (Bhagat & Carter, 2010; de Boer, Thornton, & Krumbholz, 2012; Guinan, 2006; Micheyl & Collet, 1996; Mishra & Lutman, 2014). Some studies show that the MOC unmasking function is reduced in individuals with listening difficulties (Garinis, Glattke, & Cone-Wesson, 2008; Muchnik et al., 2004; Sanches & Carvallo, 2006; Yalçinkaya, Yilmaz, & Muluk, 2010), while others do not (Burguetti & Carvallo, 2008; Butler, Purcell, & Allen, 2011; Clarke, Ahmmed, Parker, & Adams, 2006; Veuillet, Magnan, Ecalle, Thai-Van, & Collet, 2007). Thus there is no clear consensus on MOC function in APD. However, it should be noted that investigations in APD assaying the MOC have only investigated gross changes in OAE level. MOC mediated change in other cochlear attributes such as tuning remain unrecognized. Subtle discrepancies in cochlear processing due to MOC activation may be reflected better in a tuning metric, and thus may augment findings of OAE level changes. Therefore, we chose to measure MOC inhibition of SFOAE level and tuning to characterize MOC functioning in children with APD in the present study. SFOAEs are generated from a narrow site on the basilar membrane and can

be evoked at low stimulus levels (Shera & Guinan, 1999). Both these properties are important to delineate confounding factors such as middle ear muscle reflex (MEMR) from a true MOC effect (Guinan, Backus, Lilaonitkul, & Aharonson, 2003). Further, relationships between a tuning metric and MOC functioning were also probed.

5.2 Method

5.2.1 Participants

Sixty three children in the age range 7-17 years took part in the study. Thirty eight children were referred to our in-house Audiology clinic with listening problems (suspected APD group: sAPD, mean age: 9.79 years, standard deviation (SD): 2.99 years, 8 females) and twenty five were typically developing children with no complaints in listening (TD group, mean age: 11.39 years, SD: 2.59 years, 13 females). All children had normal middle ear function as determined by clinical tympanometry (GSI-TympStar, Grason-Stadler Inc., MN) and hearing thresholds of 20 dB HL or better at octave intervals between 0.25 and 8 kHz measured using a clinical audiometer (GSI-61, Grason-Stadler Inc., MN). All children had contralateral acoustic reflex thresholds >70 dB HL for steady state broadband noise (BBN). Children also underwent a screening DPOAE measurement (Integrity v-500, Vivosonic Inc., ON) to confirm the presence of OAEs.

Children in the sAPD group underwent a test battery similar to that used by Allen and Allan (2014) that included three standard clinical tests: the Staggered Spondaic Word Test (SSW; Katz, 1998), Words in Ipsilateral Competition (WIC; Ivey, 1969) and Pitch Pattern Sequence test (PPS; Pinheiro, 1977), and two psychoacoustic tests that use adaptive procedures developed in-house for use with children: Gap Detection (GD), and Difference Limen for Frequency (DLF) and auditory brainstem response

(ABR) measures at slow (13.3 Hz) and fast rates (57.7 Hz). Tests were administered in accordance with their respective manuals and were interpreted according to published age-specific normative data. Of the 38 children in the sAPD group, 27 were diagnosed as having APD based on American Speech-Language-Hearing Association [ASHA] (2005) guidelines, i.e., scored 2 SDs below the normative expectation in at least two tests. Seven children failed in one test, and four children passed all tests. Of the 11 children who passed all or all-but-one behavioral measures, all had atypical ABR in the form of prolonged peak latencies; prolonged inter-peak latencies; or abnormal wave I-V amplitude ratio. Abnormalities in ABR have been recently reported in children suspected with APD. A recent study (Allen & Allan, 2014) showed that behavioral tests alone may not be adequate in diagnosis of APD, which supports recommendations by professional bodies (e.g., AAA, 2010). Allen and Allan (2014) found several children who passed these behavioral tests had abnormal neural encoding of sound measured using ABR and/or absent/elevated acoustic reflex thresholds. Therefore, children who passed the behavioral test battery but who had abnormal ABR were also included in the study group (sAPD) along with children diagnosed as APD.

Participants sat in a comfortable chair in a double-walled sound attenuated booth (Eckel Industries, ON) and watched a silent closed captioned movie. They were encouraged to relax, and swallow as few times as comfortable. OAEs were recorded from only one ear per participant. The ear being tested was chosen based on DPOAE amplitude obtained during the screening process. Study methods were approved by the Health Sciences Research Ethics Board of Western University, Canada. The nature of the study was explained prior to obtaining written informed assent from every participant, and informed consent from participants' parent/caregiver. Participants were compensated for their time with gift cards towards books or school supplies.

5.2.2 SFOAE measurement

Stimulus and instrumentation

All signals were generated digitally in Matlab (Mathworks, MA) at a sampling rate of 32 kHz and at a bit depth of 24. Probe-tones (f_P) 2.048 s in duration, in the frequency range 0.928 to 1.248 kHz at 16 Hz intervals and 40 dB SPL were used to evoke SFOAEs. This frequency region, approximately representing the 1 kHz region, was chosen based on empirical evidence of pronounced MOC activity (Lilaonitkul & Guinan, 2012; Zhao & Dhar, 2012). Intra-cochlear suppressor tones (f_S) corresponding to each f_P (where, f_S) = f_P + 16 Hz) with linear rise/fall ramps of 50 ms duration and 60 dB SPL in level were used according to the suppression method (Brass & Kemp, 1993; Guinan, 1990) to extract SFOAE using discrete Fourier transforms. Frequencies of all tones were adjusted to have an integer number of cycles in the analysis window. The MOC elicitor, was uniform random noise/broadband noise (BBN) presented at 60 dB SPL.

Signals were presented through a digital-to-analog converter (6289 m-series, National Instruments, TX) at a sampling rate of 32 kHz to three individual programmable attenuators (PA5; Tucker-Davis Technologies, FL) that controlled the output signal levels of the probes, suppressors and elicitors. Signals were then power amplified (SA1; Tucker-Davis Technologies, FL, USA) and fed to ER2 transducers (Etymotic Research, IL) connected to an ER-10B+ otoacoustic emission probe system (Etymotic Research, IL) that delivered the signals in the ear-canal.

The ear-canal pressure was recorded using the ER-10B+ probe system with a pre-amplifier gain of +40 dB. The recorded signal was bandpass filtered (Frequency

Devices Inc., IL) between 0.4 and 10 kHz and a gain of 20 dB was applied. The filtered signal was then digitized by an analog-to-digital converter (6289 m-series, National Instruments, TX) which applied another 6 dB of gain prior to conversion. Stimulus delivery and response acquisition was controlled using custom programs developed in LabView (National Instruments, TX). All stimuli were calibrated using a Type-2250 sound level meter (Brüel and Kjær, Denmark), and an ear simulator Type-4157 (IEC 711; Brüel and Kjær, Denmark).

SFOAE recording

To describe each stimulus, we will use the terms 'epoch', 'sweep-block' and 'sweep' (see Figure 5-1). An epoch was 1.024 s in duration and sweep-blocks were made of two consecutive epochs of the same stimulus. Multiple sweep-blocks were concatenated to create a sweep of 7.168 s in duration.

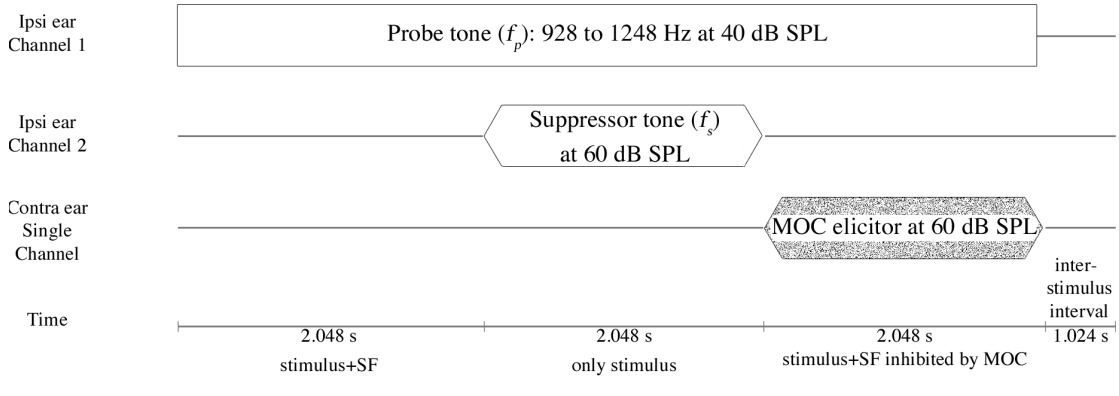

Figure 5-1: Schematic representation and temporal sequence of events for SFOAE recorded with and without MOC elicitors. Channels in the left most column indicate separate physical transducers. Note that size of each element in the figure is made disproportionate to their duration to show shorter events clearly.

One complete sweep had three sweep-blocks: 1. f_P in isolation, 2. f_P with f_S, and f_P with elicitor. A 1.024 s inter-sweep interval was used between sweeps to ensure

that the MOC reverted to its baseline activity (Backus & Guinan, 2006). An in-the-ear calibration of the tones was carried out before every measurement to produce the desired SPL (40 dB SPL) in the ear-canal. Each frequency f_P was repeated for at least five sweeps to obtain reliable SFOAEs. Additional epochs were recorded for every noisy epoch (if the epoch root-mean-square [RMS] amplitude exceeded 0 dB SPL in a 0.5 to 0.9 kHz band), for clipped epochs, or if the SNR was lower than 10 dB.

SFOAE extraction

Ear canal pressure in the first sweep-block contained both the probe stimulus, f_P, and the SFOAE as a composite mixture (P_{ECtot}). The intracochlear suppressor, f_S, was then presented in the second sweep-block, in addition to the f_P, to completely suppress the generated SFOAE (P_{ECms}) by pushing the OHCs into saturation at the f_P frequency place (Guinan, 1990). A vector subtraction of the average ear canal pressure in sweep-blocks 1 and 2 yielded the baseline SFOAE (P_{SF}), i.e., SFOAE in elicitor-off condition:

$$P_{SF} = P_{ECtot} - P_{ECms} \tag{5.1}$$

Similarly, vector subtraction of the sweep-blocks 2 and 3 yielded the SFOAE with MOC inhibition, i.e., elicitor-on condition. SFOAE stimulus levels were chosen based on previous studies (Guinan et al., 2003; Schairer, Ellison, Fitzpatrick, & Keefe, 2006) to obtain good signal-to-noise ratio (SNR) while avoiding the SFOAE stimulus from evoking any ipsilateral MOC activity. The first and last 128 ms of every response were discarded to avoid transients that may have occurred due to stimulus onset/offset. All epochs were evaluated offline using a discrete Fourier transform to obtain noise metrics in a 20 Hz band just below f_P. Epochs with noise metrics that exceeded the mean plus two SDs were not included in the average response sweep.

An SFOAE-based measure of cochlear tuning

A measure of cochlear tuning, τ, was obtained from the negative slope of the SFOAE phase gradient (rate of change of SFOAE phase as a function of frequency). This has been shown to reflect the round-trip propagation time: the time taken for f_P to reach its characteristic frequency (CF) place on the basilar membrane, and for the generated emission to return to the ear-canal (Schairer et al., 2006; Shera et al., 2002; Talmadge, Tubis, Long, & Piskorski, 1998; Zweig & Shera, 1995). The traveling wave build-up near the CF however accounts for the bulk of time during this round-trip propagation, while the ear-canal, middle-ear and basilar membrane transmission times are negligible (Don, Ponton, Eggermont, & Kwong, 1998; Zweig & Shera, 1995). For these reasons, τ, which is roughly half of the total time taken, serves as an indirect measure of cochlear tuning. The phase slope and the bandwidth (BW) of the cochlear filter at a given frequency is thus inversely related, with steeper phase slopes corresponding to sharper cochlear tuning (Shera et al., 2002). This method has been validated in several animal models (Bergevin, Freeman, Saunders, & Shera, 2008; Joris et al., 2011; Shera, Guinan, & Oxenham, 2010) and humans (Bhagat & Kilgore, 2014; Boothalingam & Lineton, 2012; Guinan et al., 2003; Schairer et al., 2006). The τ in the present study was measured in a similar fashion to Boothalingam and Lineton (2012), as in equation 5.2:

$$\tau \equiv \frac{1}{f_B - f_A} \int_B^A \tau(f)\, df \tag{5.2}$$

where, for a single frequency:

$$\begin{aligned} \tau(f) &\equiv \frac{-1}{2\pi}\frac{d\phi}{df} \\ \phi(f) &\equiv \arg\{P_{SF/stim}(f)\} \end{aligned} \tag{5.3}$$

Equation 5.2 shows the calculation of τ for frequencies (f) A to B. The first line in equation 5.3 shows how $\tau(f)$ is obtained for the frequency f. In the second line, the phase $\phi(f)$ is obtained by separating the real and imaginary parts of the SFOAE sound pressure $P_{SF}(f)$. Only the frequency regions that had SNRs better than 10 dB were considered for obtaining the group delay. This was achieved by the first author manually picking only the best SNR region; a linear regression line was then fit in that band to obtain τ. Thus a weighting function as in Boothalingam and Lineton (2012) was not required.

Spontaneous OAEs (SOAEs) were recorded to allow rejection of SFOAEs within 50 Hz of an SOAE to avoid phase related complexities.

5.2.3 Test for MEMR

In addition to confirming that ARTs for all children were >70 dB HL using a clinical immitance meter, additional analyses were performed to rule out MEMR affecting the observed MOC inhibition of SFOAE. This additional check was performed in light of several recent studies showing that MEMR can be activated at levels much lower than what is typically obtained with a clinical immitance meter (e.g. Goodman, Mertes, Lewis, & Weissbeck, 2013; Guinan et al., 2003; Zhao & Dhar, 2009). The present test is based on the hypothesis that a significant MEMR would consistently increase probe-tip stimulus levels. This is because MEMR activation will stiffen the ossicular chain and retract the tympanic membrane, resulting in increased reflection of stimulus energy back to the ear-canal. A cut-off value of 1.4% (0.12 dB) increase

in stimulus level during elicitor-on condition compared to no-elicitor condition has been suggested as an indication of MEMR activation (Abdala, Dhar, Ahmadi, & Luo, 2014; Abdala, Mishra, & Garinis, 2013).

To test for such changes in level, 55 dB peSPL clicks presented at 41.67 Hz were used as probe stimuli. Clicks were recorded in the ear-canal in two conditions, one without any contralateral elicitor and one with the same contralateral elicitor used in the study to elicit MOC reflex. RMS levels of the ear-canal recorded clicks in a time-window near the first trough of the click waveform (125 μs duration) for elicitor-on/off conditions for every participant were obtained.

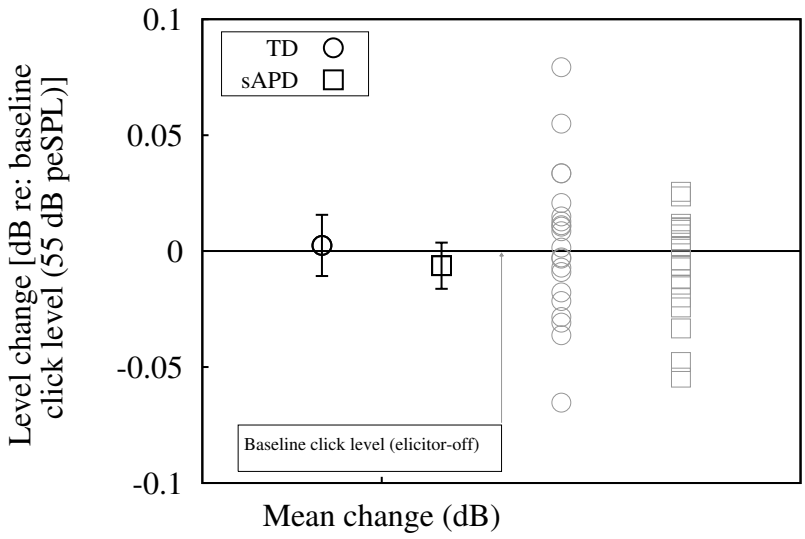

Figure 5-2: Results of MEMR test. Means and their corresponding individual data for the change in stimulus level with reference to baseline no-elicitor condition (dB) is plotted (Y-axis). Black straight line in plot A at 0 dB represents normalized baseline stimulus level (in no-elicitor condition). Black symbols are group means with their corresponding 95% confidence intervals represented by error bars. Grey symbols are individual means of RMS amplitude near the stimulus trough. Circles represent TD and boxes represent sAPD.

As seen in Figure 5-2A, changes in the presence of MOC elicitors were on average

-0.0019 dB ±0.008 (re: baseline no-elicitor). The largest change in both directions (increase and decrease in amplitude) was <0.08 dB. Observed stimulus level deviations occur in both directions, i.e., increase and decrease in level. The observed changes are small compared to level changes that would be expected if the MEMR was activated, i.e., <1.4% (0.12 dB) (Abdala et al., 2014, 2013). These changes probably arise due to random fluctuations in background noise. Note that five children (1 from TD, and 4 from sAPD group) did not undergo this secondary MEMR test due to time constraints. Therefore, in these children, their ART thresholds were used for the evaluation of MEMR activation.

5.2.4 Data inclusion criteria

For data to be considered for statistical analyses the following criteria had to be met: (1) <10% epoch rejection, (2) minimum SNR of 10 dB, and (3) no MEMR activation. Based on the inclusion criteria, 18 participants (15 from the sAPD group and 3 from the TD group) were rejected from the study either due to excessive participant-related artifacts leading to unreliable SFOAE estimates, or poor SNR. This led to inclusion of 22 participants in the TD and 23 in the sAPD group. Rejected data are considered in again in the discussion section to explore reasons for rejection in detail.

5.3 Results

Mean SFOAE level for elicitor-on and elicitor-off conditions across groups are plotted in Figure 5-3A. Examples of phase slopes, steep and shallow, one from each group are presented in Figure 5-3B. Visual examination of Figure 5-3A shows that SFOAE level is reduced in both groups with elicitor-on. To examine if the magnitude of inhibition is different between the two groups, statistical analyses were carried out.

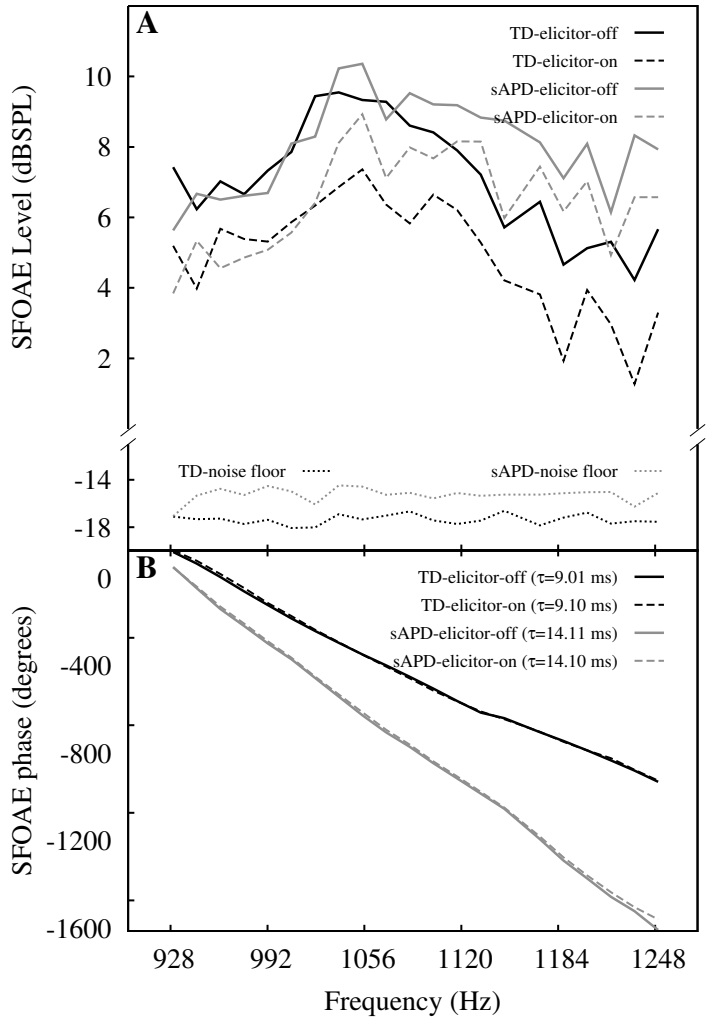

Figure 5-3: Panel-A shows mean (averaged across participants) SFOAE level as a function of frequency. Groups are indicated by colours (black for TD and grey for sAPD). In panel-B SFOAE phase slopes for two children, one from TD and one from sAPD group, for elicitor-off and elicitor-on conditions are shown. The two phase gradient examples illustrate differences in the obtained τ. In both plots, straight lines indicate elicitor-off, and dashed lines indicate elicitor-on condition.

One-way repeated measures analysis of variance (RM-ANOVA) with 'elicitor condition' (elicitor-on/off) as the independent variable and 'measure' (SFOAE level or τ) as the dependent variables were performed with group (TD and sAPD) as the grouping variable. Results show a significant interaction between elicitor condition and group for both level ($F[1,43] = 6.76$, $p = 0.013$, $\eta^2{}_{Partial} = 0.14$), and τ ($F[1,43]$

$= 5.05$, $p = 0.030$, $\eta^2{}_{Partial} = 0.11$).

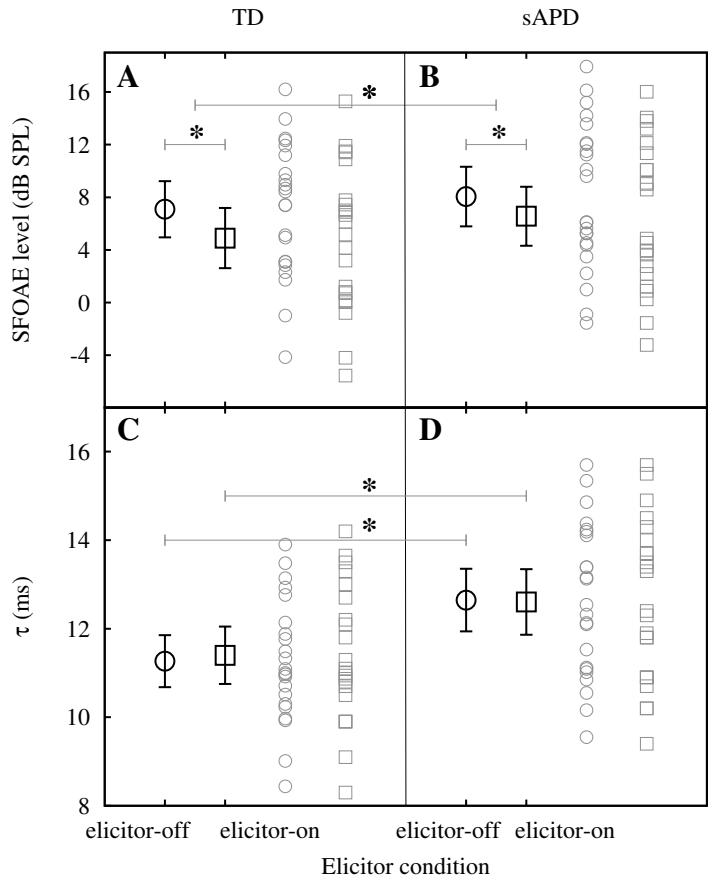

Figure 5-4: Panels A and B show mean SFOAE level (averaged across participants and frequencies) for TD and sAPD groups respectively. Error bars around the mean are 95% confidence intervals. Matching grey symbols are raw data. Panels C and D show mean τ for both TD and sAPD groups respectively. In both panels open circles represent elicitor-off condition and open boxes represent elicitor-on condition. Significant mean differences are marked with asterisks.

Post-hoc analyses with correction for multiple comparisons using the false discovery rate (FDR: Benjamini & Hochberg, 1995) indicate significant inhibition of SFOAE level by elicitor in both TD (Mean difference [MD] = 2.19 dB (21.71% change), $CI_{95\%} = \pm 0.51$ dB, $t[21] = 9.01$, $p<0.001$), and sAPD groups (MD = 1.49 dB (15% change), $CI_{95\%} = \pm 0.40$ dB, $t[22] = 11.83$, $p<0.001$). However, as illustrated in the

top panels of Figure 5-4 (A and B), SFOAE level change was significantly higher in the TD group compared to the sAPD group (MD = 0.70 dB (6.13%), $CI_{95\%} = \pm 0.55$ dB, $t[43] = 2.60$, $p = 0.013$). This suggests weaker MOC functioning in the sAPD group.

The bottom panels of Figure 5-4 (C and D) illustrates significantly longer τ in the sAPD group as compared to the TD group (MD = -1.38 ms, $CI_{95\%} = \pm 0.95$ ms; $t[43] = -2.92$, $p = 0.006$), suggesting sharper tuning in the sAPD group. Mean τ in the TD group was 11.27 ms, and it was 12.64 in the sAPD group.

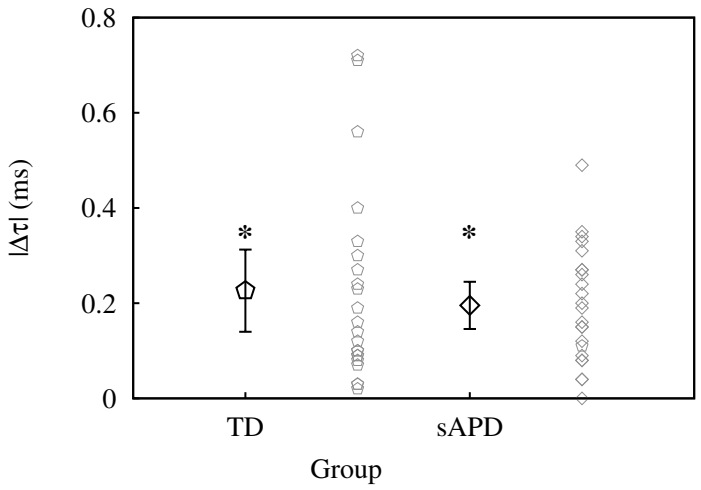

Figure 5-5: Symbols in black show absolute mean change in τ ($|\Delta\tau|$) for TD and sAPD groups, and their corresponding raw data are shown in grey symbols. Error bars represent 95% confidence interval. Asterisks indicate significant change in τ in elicitor-on condition from baseline elicitor-off condition.

τ in elicitor-on condition was also significantly different between groups (MD = -1.21 ms, $CI_{95\%} = \pm 1.02$ ms, $t[43] = -2.40$, $p = 0.021$). Unlike the MOC mediated change in level, change in τ was in both directions, i.e., both increase, and decrease in delay from elicitor-off condition were observed across participants. Simple averaging

of this bidirectional change may not represent the actual MOC mediated change in tuning. Therefore, mean of the absolute change in delay was obtained for both groups, as shown in Figure 5-5.

Single-sample FDR corrected t-tests show that τ was significantly altered by the MOC in both TD (Mean = 0.23 ms, $CI_{95\%} = \pm 0.09$ ms, $t[21] = 5.14$, $p<0.001$) and sAPD (Mean = 0.20 ms, $CI_{95\%} = \pm 0.04$ ms, $t[22] = 7.72$, $p<0.001$) groups. This result appears to contradict two previous reports on MOC induced change in SFOAE group delay (Bhagat & Kilgore, 2014; Boothalingam & Lineton, 2012). Both these studies did not find a significant change in SFOAE group delay due to MOC inhibition. However, both these studies averaged their raw phase gradient change across participants. Due to the bidirectional nature of change in the tuning metric across participants, perhaps an absolute measure is appropriate to understand the role of MOC strength on tuning. However, individual data or regression analysis may be more appropriate if one were to study the direction of change. The absolute MOC mediated change in τ, i.e., $|\Delta\tau| = |\tau(elicitor_{off}) - \tau(elicitor_{on})|$, was not significantly different between groups (MD = 0.031 ms, $CI_{95\%} = \pm 0.10$ ms, $t[43] = 0.62$, $p = 0.53$). Mean τ of 11.27 ms and 11.40 ms equate to filter BWs of 78.71 and 78.16 Hz, in elicitor-off and elicitor-on conditions, respectively in the TD group. In the sAPD group, mean τ of 12.64 ms and 12.60 ms equate to bandwidths of 70.37 and 70.74 Hz in elicitor-off and elicitor-on conditions. Group delay was converted to filter bandwidths using the method of Shera et al. (2002). These results suggest sharper tuning in children in the sAPD group compared to the TD group.

To investigate relationships between cochlear tuning and MOC functioning, a normalized measure of MOC strength (ΔSFn) was subjected to correlation analysis with tuning measures. ΔSFn is the percent change in SFOAE level from elicitor-off condition to elicitor-on condition, normalized by baseline SFOAE level at each frequency

in Pascals (Garinis, Glattke, & Cone-Wesson, 2011; Mishra & Lutman, 2013).

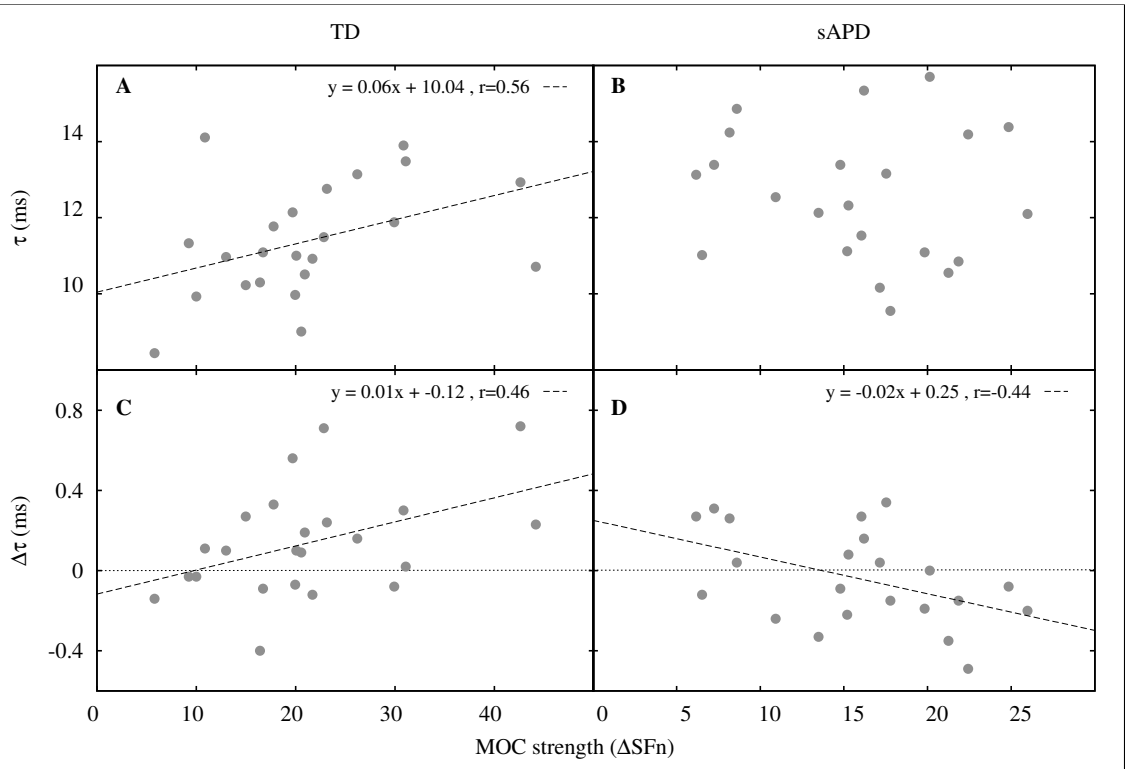

Figure 5-6: Panels A and B show correlation between ΔSFn and τ for TD and sAPD groups, respectively. Note that the correlation was significant only in the TD group. Panels C and D show correlation between ΔSFn and $\Delta\tau$ for TD and sAPD groups, respectively. In panels A, C, and D, dashed diagonal lines represent the relationship between variables in x- and y- axes and the corresponding equation is shown on the top right corner in each panel. Note that the x-axis is different for TD and sAPD groups, owing to greater MOC strength in the TD group. In panels C and D, dotted horizontal line at 0 represents no change in τ due to MOC inhibition. Data points above the line represent increase in cochlear delay, and data points below the line represent decrease in cochlear delay due to MOC activation. Notice that most children in TD group are above the 0 change line and the opposite is true in the sAPD group.

As illustrated in Figures 5-6A and 5-6B, correlation between ΔSFn and τ (in quiet) was significant in the TD group (Pearson $r[19] = 0.56$, $p = 0.006$) but not in the sAPD group (Pearson $r[20]$ = -0.14, $p = 0.52$). However, with elicitor-on, correlations between ΔSFn and $\Delta\tau$ were significant for both TD (Pearson $r[19] =$

0.46, p = 0.031), and sAPD groups (Pearson r[20] = -0.44, p = 0.035), albeit in opposite directions (Figures 5-6C and 5-6D). This may suggest that MOC inhibition sharpens cochlear tuning in the TD and broadens tuning in the sAPD group.

5.4 Discussion

The objective of this study was to: (1) investigate cochlear tuning, (2) reconcile MOC functioning, and (3) explore the relationship between cochlear tuning and MOC functioning in children with listening problems (sAPD).

5.4.1 Cochlear tuning

The τ obtained for the TD group in the current study (11.27 ms) is consistent with adult data reported in a previous study for the same frequency (1 kHz) region (Shera & Guinan, 2003). However, children in the sAPD group have significantly longer SFOAE delay (12.64 ms), indicative of sharper cochlear tuning. This result may appear counterintuitive at first, because individuals with sharper cochlear tuning would typically be expected to demonstrate good listening (Glasberg & Moore, 1986; B. C. J. Moore, 2003a; Oxenham & Shera, 2003; Shera et al., 2002). However, it should be noted that fine frequency resolution comes at the cost of temporal resolution. A significantly longer τ in the sAPD group could potentially affect their auditory processing in many ways. First, filter theory dictates that a sharper filter will ring longer (Oppenhiem and Wilsky (1997) cited in: Francis & Guinan, 2010). Consequently, filter ringing in the sAPD group (2.29 ms) is longer than the TD group (2.02 ms), where ringing duration is obtained from the BW of the filter using the formula: $1/(2*\pi*BW)$ (Hamilton, 2007). This seemingly small difference in ringing between the two groups ($\sim$250 μs) can be considered large in the auditory realm, especially for localization where humans have been shown to discriminate sounds oc-

curring as small as 10 μs apart (Yost, 1974). Longer ringing time in the sAPD group thus has the potential to affect their localization acuity (Wakeham, 2008; Zakaria, 2007).

Secondly, in addition to a linear response such as filter ringing, a frequency specific cochlear non-linearity driven basilar membrane response called 'after-vibrations' is also shown to be sensitive to cochlear filter gain and delay (Zheng et al., 2011). After-vibrations are basilar membrane motions that persist for tens of milliseconds after stimulus cessation. A sharper cochlear filter will thus ring longer and produce longer lasting after-vibrations, increasing forward masking. In fact, Shailer and Moore (1983) reported an inverse relationship between filter bandwidth and gap detection threshold for frequencies 1 kHz and below in adult listeners. These authors suggested that ringing of the auditory filter would partially fill in the gaps in a gap detection task, limiting temporal acuity. Cochlear contributions to forward-masking has also been reported (Oxenham & Plack, 2000). In a typical speech discourse, speech sounds occur in rapid succession and an increase in forward masking can mask speech contrasts, affecting overall speech perception (Dubno, Horwitz, & Ahlstrom, 2003), especially for lower frequencies where filter ringing is more prominent. It is thus possible that sharper cochlear tuning in children with sAPD may affect their auditory temporal acuity, and in turn, speech perception and other related auditory processes. A closer look at the results of our APD test battery shows that 12 out of 23 children (sAPD group) failed in the Gap Detection Test, suggesting difficulties in temporal processing in half the sample. However, there was no correlation between gap detection thresholds and τ. This is not surprising given the restricted range in τ (9.55 to 15.7 ms) in comparison to a much larger range in gap detection thresholds (4.55 to 60.44 ms). Also, behavioral measures of temporal acuity involve coordination of several neural mechanisms and may be influenced by non-auditory factors (Allen &

Allan, 2014).

Processing aberrations at the periphery can likely cause a cumulative effect that may alter signal integrity at higher levels of the auditory system. For instance, given cochlear influences on auditory brainstem responses (Dhar et al., 2009; Nuttall, Heinrich, Moore, & de Boer, 2013), it can be envisaged that atypical cochlear processing could have a bearing on some of the timing deficits reported at the brainstem level in children with listening problems (Hornickel & Kraus, 2013; Skoe & Kraus, 2010; Warrier, Johnson, Hayes, Nicol, & Kraus, 2004). Further, temporal processing deficits have long been suggested to affect normal development of the phonological system (Tallal, 1980; Tallal, Miller, & Fitch, 1993) and are evident in reading disability (Reed, 1989), although with no clear consensus (Bishop, Carlyon, Deeks, & Bishop, 1999). Nevertheless, the importance of temporal processing in language development (Benasich & Tallal, 2002; Trehub & Henderson, 1996) and speech perception (Dubno et al., 2003; B. C. J. Moore, 2003a; Phillips, 1999) is well established. Given the commonly observed co-morbidity of reading/learning difficulties in children with listening difficulties (Sharma, Purdy, & Kelly, 2009), it can be asserted that atypical cochlear tuning may have some bearing on their global auditory processing deficits. It should be noted that there is considerable overlap in the delay metric between the two groups. This means that not all children with listening difficulties will have sharper tuning, but perhaps a subset of APD may have listening difficulties arising due to atypically sharp tuning. Identifying children with known physiological processing differences, such as cochlear tuning, and profiling their auditory behavior may shed more light on the influence of subtle physiological differences in children with APD.

Some caveats to consider are middle-ear transmission differences across the age

group tested in this study. However, considering there was no age effect in the tuning metric obtained, this middle-ear effect can be largely ruled out. Another variable may be level differences across individuals, this variable too was accounted for with the use of individualized in-ear calibration at every frequency. thus even if there were ear-canal size differences or probe insertion depth differences, they were accounted for. In addition, a 10 dB SNR criterion was used in this study to avoid contamination of phase responses due to noise. Although this high SNR criterion led to rejection of many children, the remaining sample can be considered with confidence. Thus the stimulus level reaching the cochlea can be assumed to be homogeneous across the sample, therefore, the difference in tuning metric observed can only be attributed to the difference in actual cochlear tuning.

5.4.2 MOC function and cochlear processing

Significantly lower MOC strength in the sAPD group is consistent with previous studies (e.g., Muchnik et al., 2004), and is suggestive of reduced MOC functioning. It is possible that this reduced MOC functioning may contribute to speech-in-noise difficulties in children with sAPD. Further, the presence of correlation between τ and ΔSFn in the TD group and the lack of which in the sAPD group indicates that the MOC influence is important for normal functioning of the cochlea, even in quiet. It is enticing to interpret reduced MOC control on the cochlea in the sAPD group as responsible for their elevated cochlear tuning. However, as seen in Figure 5-6A, the direction of correlation in the TD group suggests otherwise: stronger MOC reflex was associated with sharper cochlear tuning. It is important to note the relationship between MOC reflex and τ exists in the absence of an MOC elicitor. One possible reason for this correlation could be the pre-natal relationship between the MOC and the developing cochlea. Transient MOC innervation on the inner hair cells has been shown to be critical for proper development of the auditory system (Johnson et al.,

2013; Lauer & May, 2011; Simmons, 2002).

E. J. Walsh, McGee, McFadden, and Liberman (1998) reported broader tuning curves resulting from improper development of the cochlear amplifier in neonatally de-efferented cats. These investigators also suggested that the de-efferentation could lead to either over- or under- expression of a key component of the OHC amplification process. However, it is unknown if 'reduced', as opposed to complete loss of, MOC activity during developmental stages in the sAPD group could lead to the subtle irregularities observed in their cochlear processing. Another related reason is based on maturity of non-linear cochlear processing. OAE-based studies report adult like intra-cochlear suppression tuning curves in full-term neonates (Abdala, Sininger, Ekelid, & Zeng, 1996; Bargones & Burns, 1988; Chabert et al., 2006; Eggermont, Brown, Ponton, & Kimberley, 1996), providing support for cochlear maturity at birth. However, pre-term neonates show sharper cochlear tuning than full-term neonates and adults for frequencies below 1.5 kHz (Abdala et al., 1996). This unusually sharp tuning has been unexplained by middle-ear transmission differences across age groups (Abdala & Dhar, 2012; Abdala, Keefe, & Oba, 2007). In addition, Abdala and Chatterjee (2003) reported that the DPOAE input/output function in immature cochleae shows saturation at very high levels compared to adults, suggesting an extended range, and 'over-activity' in cochlear amplification. Basilar membrane immaturity in the apical half of the cochlea (Abdala & Dhar, 2012) and immature MOC (Abdala, 2000) have been suggested as possible causes for such atypical processing. Evidence for immature MOC activity has also been reported by Abdala et al. (2013), where pre-term neonates showed persistent DPOAE level enhancement that is unrelated to DPOAE source mixing. Sharper tuning observed in the sAPD group in the current study is similar to the sharper-than-normal tuning observed in cochleae that are thought to be immature. Reduced MOC control on cochlear ampli-

fication, and the lack of correlation between τ and ΔSFOAE support the hypothesis that cochlear processing discrepancies observed in the sAPD group could stem from reduced MOC functioning with potential developmental links.

An intriguing result from the current study is the opposing correlation between ΔSFn and $\Delta\tau$ between groups. While MOC activation sharpens cochlear tuning in the control group, it appears to broaden cochlear tuning in the sAPD group. Considering MOC activation reduces cochlear gain, a broadened cochlear filter is expected according to filter theory (Francis & Guinan, 2010). However, the increase in tuning found in the control group is consistent with previous studies for the 1 kHz region (Bhagat & Kilgore, 2014; Francis & Guinan, 2010). Using afferent fiber tuning curves in cats, Guinan and Gifford (1988) showed sharpened tuning elicited by MOC activation at low frequencies (<2 kHz) due to an increase in the threshold of the low frequency side of the tuning curve. At frequencies above 2 kHz, broadened tuning occurred due to an increase in threshold *at* the CF, i.e., at the tip of the tuning curve. This difference in MOC activation is suggestive of differential cochlear amplification between low and high frequency regions on the basilar membrane (Cooper & Rhode, 1995; Ruggero, Rich, Recio, Narayan, & Robles, 1997). Similar results have also been reported for psychoacoustic tuning curves (Aguilar, Eustaquio-Martín, & Lopez-Poveda, 2013; Kawase et al., 2000; Quaranta, Scaringi, Nahum, & Quaranta, 2005; Vinay & Moore, 2008). MOC inhibition of SFOAEs has thus revealed a difference in the cochlear amplification process for the sAPD group, in addition to their sharper tuning. Collectively, the differential cochlear amplification and overactive cochlea appear to provide reasoning for both atypically sharp tuning and the tendency towards broadening of tuning with MOC activation.

$\Delta\tau$ in the TD group suggests that the MOC may aid in maintaining broad tuning

in quiet which promotes better temporal resolution. In the presence of background noise, MOC inhibition of OHC activity sharpens cochlear tuning, promoting better spectral resolution, at least at 1 kHz. Both frequency and temporal resolution are critical for optimal auditory processing. Therefore, it can be envisaged that reduced MOC functioning in the sAPD group may lead to difficulties in auditory processing, due to forward masking, and reduced signal unmasking in noise. Improper signal processing can lead to development of a weak phonological system in children (Tallal, 1980). This may in turn fail to fine-tune the auditory system in selectively responding to meaningful speech stimuli (Hornickel & Kraus, 2013), with consequent auditory and reading/learning difficulties. It is currently unknown how much such an adaptive change in tuning can influence auditory processing further up the auditory system. Further studies that investigate other auditory processes in conjunction with the MOC and cochlear functioning may provide additional insights into the MOC and cochlear role in the difficulties presented by children with sAPD.

5.4.3 What about rejected data?

Considering many of the children whose data were rejected belonged to the sAPD group (15 out of 18), rejected data were examined for common factors for rejection among sAPD children. All children whose data were rejected passed the screening DPOAE test, therefore were expected to have good SFOAEs. Indeed, many children did have good SFOAEs. However, SFOAE group delay calculation is derived from measures at multiple discrete frequencies. Therefore, if some frequencies are affected by noise or artifacts, the SFOAE group delay calculation will be unreliable. This is because, the group delay calculation requires a reliable estimate of the slope of the regression line fitted to the phase data. If some frequencies are affected by large artifacts, it will render the resulting slope unreliable. This happened in 7 of 15 sAPD children who were rejected.

Further, average noise floor level in the 13 of 15 children (data from two children could not be used due to excessive artifacts) that were rejected was -12 dB SPL, with some as high as -3 dB SPL, compared to -17 dB SPL in TD children who were included in the study. Pairwise comparison of noise levels between children rejected from the sAPD group and TD children revealed a significant difference between these groups (t[15.06] = -3.54, p = 0.003). This suggests that children with listening problems can also be quite noisy. Sources of this noise may be due to an inability to follow instruction to sit quietly, causing artifacts, or some were unable to sit quietly even if they understood instructions. These factors point towards distractibility of these children, and may have implications in an academic setting. A few children who were able to sit quietly had excessive physiological noise such as breathing and circulatory sounds. K. P. Walsh, Pasanen, and McFadden (2014) suggested that MOC activity mediated by attention may be involved in reducing ear-canal physiological noise. Together, reduced MOC activity and co-morbidities that may be related to inattention (D. R. Moore, Ferguson, Edmondson-Jones, Ratib, & Riley, 2010) may also contribute to excessive noise in the sAPD group. Higher rejection in the sAPD group thus calls for two things; (1) further examination of aspects such as internal physiological noise that may or may not be associated with the auditory system, (2) development of tools that are resilient to physiological noise and participant related artifacts to measure cochlear tuning and MOC inhibition of OAEs.

5.5 Conclusion

Results from the current study show atypically sharp cochlear tuning and reduced MOC functioning in children with listening difficulties. Increased tuning causes longer cochlear filter ringing times and increased after-vibrations that can potentially affect

temporal processing ability. However, there were overlap in data between the two groups, suggesting that not all children with suspected APD will have sharper cochlear tuning, but perhaps a subset of children with suspected APD may have listening difficulties arising due to sharper-than-optimal cochlear tuning. Correlation between tuning in quiet and MOC reflex in the TD group, and the lack of this in the suspected APD group suggests that MOC is important for normal functioning of the cochlea. The change in cochlear tuning in opposite directions (sharper in TD, and broader in sAPD) due to MOC activation shows contrastive cochlear function between the two groups. Collectively, differential cochlear amplification, reduced MOC function, and significantly sharper tuning may be interlinked in the findings of the sAPD group. Further studies are required to explore auditory processes that could be influenced by such subtle differences in cochlear processing and MOC functioning in children suspected with APD.

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Chapter 6

Binaural Medial Olivocochlear Functioning in Children with Suspected Auditory Processing Disorder

6.1 Introduction

It is now well known that cortical influence on peripheral hearing mechanisms fine tunes bottom-up signal encoding (Khalfa et al., 2001; León, Elgueda, Silva, Hamame, & Delano, 2012; Perrot et al., 2006; Winer, 2006; Xiao & Suga, 2002). The final leg in this feedback loop is the medial olivocochlear system (MOC) at the level of the superior olivary complex (SOC). Cortico-olivary projections contact the MOC directly (Coomes & Schofield, 2004; Mulders & Robertson, 2000), or through indirect connections that traverse via various collicular nuclei (Huffman & Henson, 1990). This top-down influence has been shown mainly to regulate the gain of bottom-up signals in the system (Robinson & McAlpine, 2009). This gain regulation starts from the cholinergic MOC axons that directly innervate the electromotile outer hair cells (OHCs) in the cochlea (Gifford & Guinan, 1987; Liberman & Brown, 1986; Warr & Guinan, 1979). Upon activation, the MOC hyperpolarizes OHC activity thereby reducing the putative cochlear amplification (Guinan, 2006), measured as

reduced afferent neural responses (Guinan & Gifford, 1988) and otoacoustic emissions (OAEs; Collet et al., 1990; Guinan, 2006). This reduction in OHC activity improves the dynamic range of afferent fibers in noise, such that they can fire for novel transient stimuli, essentially improving the signal-to-noise ratio (SNR; Kawase, Delgutte, & Liberman, 1993; Winslow & Sachs, 1988). Improvement in SNR translates to better speech perception in noise (de Boer, Thornton, & Krumbholz, 2012; Giraud et al., 1997; Kumar & Vanaja, 2004; Mishra & Lutman, 2014). Improvement in speech-in-noise is relevant to the present study because, it is the prime issue in children with auditory processing disorder (APD), despite their normal hearing thresholds (Chermak, Tucker, & Seikel, 2002).

American Academy of Audiology [AAA] (2010) defines APD as "difficulties in the perceptual processing of auditory information in the central nervous system and the neurobiological activity that underlies the processing". Impetus for investigation of MOC strength (magnitude of reduction in OAE level) was provided by recent studies that show reduced MOC function in children with APD (Muchnik et al., 2004; Sanches & Carvallo, 2006), selective mutism (Bar-Haim et al., 2004) and adults with learning difficulties (Garinis, Glattke, & Cone-Wesson, 2008). On the other side of the 'listening' spectrum, musicians show stronger than typical MOC strength (Brashears, Morlet, Berlin, & Hood, 2003; Micheyl, Khalfa, Perrot, & Collet, 1997; Perrot, Micheyl, Khalfa, & Collet, 1999). Considering musicians show exceptional listening abilities (review: Perrot & Collet, 2013), strong MOC reflex in musicians, and weak MOC reflex in individuals with poor speech-in-noise perception makes a strong argument towards MOC's role in fine-tuning the auditory system, especially in noise. These studies have led to speculation that MOC inhibition, and/or reduced corticofugal influence on the cochlea could play a role in speech-in-noise problems in children with listening difficulties. However, there is no clear consensus on the MOC

inhibition of OAEs in APD. Some studies have failed to find any difference in MOC function between typically developing (TD) children and children with APD (e.g., Butler, Purcell, & Allen, 2011).

It should also be noted that Sanches and Carvallo (2006) too did not find a significant group difference in MOC inhibition; inhibition in their APD group was numerically smaller when it was expressed as a percentage of control group inhibition. Muchnik et al. (2004) found statistically significant group differences, and also reported that fewer children in their control group had MOC inhibition that was smaller than a cut-off value (0.6 dB or 1 dB) compared to their APD group in an equality of proportions test. It is thus unclear, if MOC function is truly reduced in children with APD. Moreover, MOC-based studies in individuals with listening difficulties have only used contralateral stimulation of the MOC so far; this only evokes the uncrossed MOC pathway (Guinan, 2006; Warr & Guinan, 1979). Anatomically, the contralateral stimulus crosses midline and evokes 'contra' MOC neurons (re: MOC monitoring probe ear) which project to the ipsilateral ear without crossing the midline. An ipsilateral stimulus on the other hand, crosses the midline and evokes 'ipsi' MOC neurons; axons from ipsi neurons cross the midline again (double-crossed) and project back to the ipsilateral cochlea (Guinan, 2006; Warr, 1992).

Listening in noise in real life will evoke both these crossed and uncrossed MOC pathways through binaural activation. In addition, a large proportion of MOC neurons respond to binaural stimuli (Brown, Kujawa, & Duca, 1998; Liberman, 1988; Liberman & Brown, 1986). Several differences in physiological responses between monaural and binaural MOC activation have been reported. For instance, binaural MOC activation is more effective in protecting the cochlea against loud noises (Rajan & Johnstone, 1988). MOC inhibition also alters cochlear tuning; if both cochleae are

not adjusted in tandem, auditory process such as localization, that depend on subtle timing differences between ears, can be disrupted (Francis & Guinan, 2010). Thus, if one were to elucidate MOC function in children with APD, binaural MOC activity must be studied.

The present study sought to address this by measuring ipsilateral (crossed), contralateral (uncrossed) and binaural (both crossed and uncrossed) MOC activation of MOC in children with suspected APD. Another motivation for studying binaural MOC function in this population is that, children with APD have also been indicated to have inconsistencies in binaural signal processing (American Academy of Audiology [AAA], 2010; Delb, Strauss, Hohenberg, & Plinkert, 2003; Gopal & Pierel, 1999; Sweetow & Reddell, 1978). Sweetow and Reddell (1978) reported reduced binaural masking level difference (BMLD) in children with APD.

Reduced BMLD has also been indicated in children with a history of otitis media, typically considered at risk for APD (Hall & Grose, 1993; Moore, Hutchings, & Meyer, 1991). In addition to reduced BMLD, reduced binaural interaction measured using behavioral tests such as binaural resysnthesis have also been reported in children with listening difficulties (Roush & Tait, 1984). Physiological measures such the auditory brainstem response (ABR) binaural interaction component (BIC) have also been reported to be affected in children with APD (Delb et al., 2003; Gopal & Pierel, 1999). Obtaining ipsilateral, contralateral and binaural MOC inhibition of OAEs presents an opportunity to study binaural interaction at the level of the MOC in children with APD. However, note that fundamental differences exist between the electrophysiological BIC (eBIC), an afferent response, and an MOC counterpart of eBIC (mBIC), an efferent response measured acoustically. Nevertheless, mBIC may provide insights into both MOC function and its binaural interaction in these

children. Thus, a secondary aim of this study was to explore mBIC in children with APD. Where, mBIC is the difference between the sum of ipsilateral and contralateral MOC inhibition of OAEs and binaural MOC inhibition of OAEs:

$$mBIC = (ipsi + contra)MOCinhibition - binauralMOCinhibition \tag{6.1}$$

A positive mBIC would mean binaural inhibition$_A$[1] because the response to binaural stimulation would be smaller than the sum of monaural responses. A negative mBIC would mean binaural facilitation, as binaural response would be larger than the sum of monaural responses. In addition to the mBIC, binaural resysnthesis (BR; Ivey, 1969), a behavioral test, was also conducted to obtain a behavioral correlate of binaural interaction. BR involves dichotic presentation of two words, where information to one ear is low-pass filtered, and words presented to the opposite ear is high-pass filtered. The listener's task is to repeat the correct word by integrating information from both ears. This has been shown to be an effective test in diagnosis of APD in children (Singer, Hurley, & Preece, 1998). In summary, binaural MOC function, and binaural interaction obtained using MOC inhibition of OAEs, and a behavioral measure of binaural interaction was investigated in children with suspected APD in the present study.

6.2 Method

6.2.1 Participants

Forty-seven children in the age range 7-17 years, twenty-one TD children (TD group; mean age = 11.4 years, standard deviation (SD) = 2.4 years, 13 females) and twenty-

[1]In order to avoid confusion between binaural neural *inhibition* at the brainstem level and MOC *inhibition* of CEOAEs, we will refer to binaural neural inhibition as inhibition$_A$ (subscript 'A' refers to afferent pathway). Note that these terms are descriptive (McPherson & Starr, 1993).

six children referred to our in-house Audiology clinic with listening problems took part in the study (sAPD group; mean age = 9.9 years, SD = 2.8 years, 8 females). All children had normal middle ear function and hearing thresholds of 20 dB HL or better between 0.25 and 8 kHz at octave intervals. All children had ipsilateral and contralateral acoustic reflex thresholds >70 dB HL for steady state broadband noise (BBN). Children also underwent a screening DPOAE measurement (Integrity v-500, Vivosonic Inc., ON) to confirm the presence of OAEs.

Children in the sAPD group underwent a test battery similar to that used by Allen and Allan (2014) that included three standard clinical tests: the Staggered Spondaic Wordlist (SSW; Katz, 1998), Words in Ipsilateral Competition (WIC; Ivey, 1969) and Pitch Pattern Sequence test (PPS; Pinheiro, 1977), and two psychoacoustic tests that use adaptive procedures developed in-house for use with children: Gap Detection (GD), and Difference Limen for Frequency (DLF). Tests were administered in accordance with their respective manuals and were interpreted according to published age-specific normative data. Of the 26 children in the sAPD group, 16 were diagnosed as having APD based on American Speech-Language-Hearing Association [ASHA] (2005) guidelines, i.e., scored 2 SDs below the normative expectation in at least two tests. Eight children failed in one test, and two children passed all tests. Of the 10 children who passed all or all-but-one behavioral measures, all had atypical ABR in the form of prolonged peak latencies; prolonged inter-peak latencies; or abnormal wave I-V amplitude ratio. Abnormalities in ABR have been recently reported in children suspected with APD. A recent study (Allen & Allan, 2014) showed that behavioral tests alone may not be adequate in diagnosis of APD, which supports recommendations by professional bodies (e.g., AAA, 2010). Allen and Allan (2014) found several children who passed these behavioral tests had abnormal neural encoding of sound measured using ABR and/or absent/elevated acoustic reflex thresholds.

Therefore, children who passed the behavioral test battery but who had abnormal ABR were also included in the study group (sAPD) along with children diagnosed as APD.

The study was conducted in a double-walled, sound attenuated booth (Industrial Acoustics Company, NY). Study methods were approved by the Health Sciences Research Ethics Board of Western University, Canada. The nature of the study was explained prior to obtaining written informed assent from every participant, and informed consent from participants' parent/caregiver. Participants were compensated for their time with gift cards towards books or school supplies.

6.2.2 Otoacoustic emission experiment

Stimulus generation and recording

All stimuli were digitally generated in Matlab (Mathworks Inc, MA) at a sampling rate of 32 kHz. Clicks were unfiltered, and 93.75 μs in duration, corresponding to four sample points at 32 kHz sampling rate, and were presented at 55 dB peSPL. This level was chosen to maximize the probability of MOC inhibition (Hood, Berlin, Hurley, Cecola, & Bell, 1996; Veuillet, Collet, & Duclaux, 1991) while minimizing any ipsilateral MOC inhibition due to the stimulus clicks. In order to obtain ipsilateral and binaural MOC inhibition of CEOAEs, the present study used a forward masking paradigm. This is illustrated in Figure 6-1; the MOC elicitor was presented first to activate the MOC, and OAE evoking clicks followed after a 2 ms gap. More specifically, four click 'epochs' were presented in a sequence following MOC elicitor presentation; each epoch was 24 ms long and contained one click presentation. A train of four epochs, called a sweep-block, was 96 ms long, and corresponded to the rate 41.67 Hz. This arrangement was chosen to capture the complete MOC inhibitory effect, which has been shown to have a decay time of 159 $\pm$ 54 ms (Backus & Guinan, 2006).

MOC activating elicitors were uniform random BBN of 478 ms duration with 20 ms onset/offset ramps to avoid startle responses. Elicitors were presented at 60 dB SPL, sufficiently below the ART of every participant. Notwithstanding, additional tests (see subsection 6.2.2) were performed to check for the effect of the middle ear muscle reflex (MEMR) on click stimuli. The 2 ms gap between elicitor presentation and start of click presentation was introduced to allow any transducer ringing to subside, and the basilar membrane to revert to baseline activity to avoid intracochlear suppression.

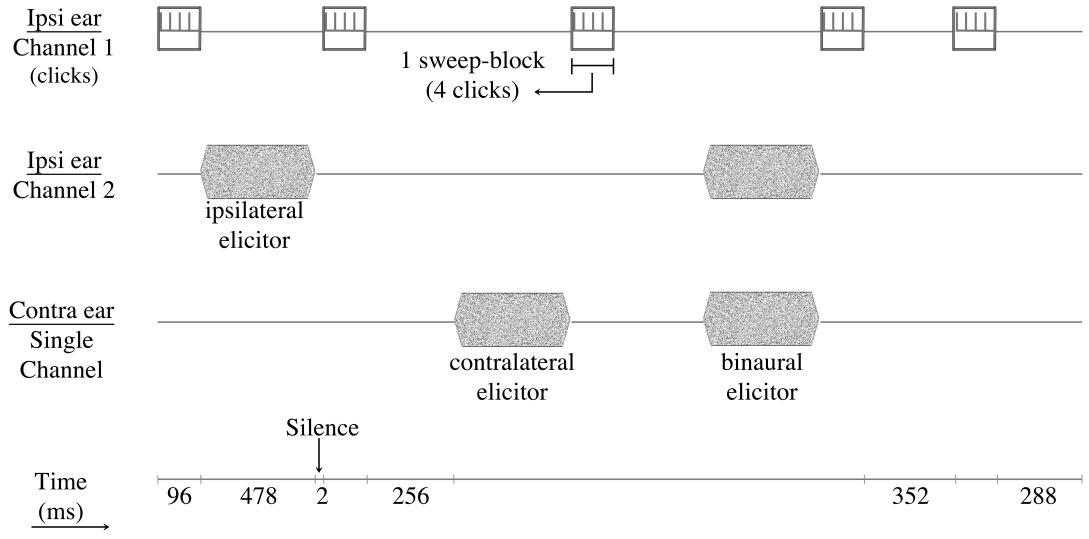

Figure 6-1: Schematic representation and temporal sequence of events for CEOAE recording with MOC elicitors. Four clicks per elicitor condition were presented to obtain CEOAE, this is depicted as squares (with clicks) on the top row. Elicitors in ipsilateral and contralateral channels are in illustrated in separate rows. Duration of each event is provided in the fourth row. Note that size of each element in the figure is made disproportionate to their duration to show smaller events clearly.

In the forward masked CEOAE paradigm, elicitors were presented ipsilaterally, contralaterally and binaurally (see Figure 6-1). Adequate silent gaps were introduced between each MOC activation so that the MOC reverted back to its baseline activity before being activated by another elicitor. A minimum duration of 200 ms is required

for these gaps (Backus & Guinan, 2006). The difference in this gap duration across sweep-blocks is to accommodate integer number of 1.024 s windows in one complete sweep, to match the restrictions of our measurement system.

Signals were played through a digital-to-analog converter (National Instruments 6289 m-series, TX) at a sampling rate of 32 kHz to three separate programmable attenuators (PA5; Tucker-Davis Technologies, FL) that controlled the output signal levels. Clicks and ipsilateral elicitors were presented in two separate channels routed to the same ear. These signals were power amplified (SA1; Tucker-Davis Technologies, FL) and fed to two ER2 transducers (Etymotic Research, IL) connected to an ER-10B+ otoacoustic emission probe system (Etymotic Research, IL) that delivered signals in the ear-canal. A single ER2 insert receiver delivered contra-elicitors in the contralateral ear. All stimuli were calibrated using a Type-2250 sound level meter (Brüel and Kjær, Denmark), and an ear simulator Type-4157 (IEC 711; Brüel and Kjær, Denmark). Responses were recorded using the ER-10B+ probe system with the pre-amplifier gain set at +40 dB. The recorded signal was then fed through a bandpass filter (Frequency Devices Inc., IL; chasis 90IP with a 90PF dual-channel programmable filter card) that filtered responses from 0.4 to 10 kHz and applied a further 20 dB gain. The filtered response was then digitized by an analog-to-digital converter which applied another 6 dB of gain prior to conversion (National Instruments 6289 m-series). Stimulus delivery and response acquisition were controlled using custom programs developed in LabView (National Instruments, TX), similar to Purcell, Butler, Saunders, and Allen (2008). The laterality of elicitor presentation was counterbalanced across participants. Participants sat in a comfortable chair in a double-walled sound attenuated booth and watched a silent closed captioned movie. They were encouraged to relax, and swallow as few times as comfortable. OAEs were recorded from only one ear per participant. The ear being tested was chosen based

on DPOAE amplitude obtained during the screening process.

CEOAE offline analyses

Stimulus reliability was checked across all recorded epochs to remove artifactual epochs. Epochs with stimulus RMS amplitudes that were two SDs above the mean (within-individual) were rejected. Responses in the time-window from 5-20 ms were extracted, and digitally bandpass filtered from 0.5 to 6 kHz using a fourth order zero delay Butterworth filter to obtain CEOAE and noise metrics. To estimate response reliability, consecutive epochs were separated into two buffers: A and B. A correlation analysis was performed between the two buffers and served as a measure of reliability. Noise was estimated by subtracting the RMS difference between the grand response mean and mean responses from each buffer. A CEOAE was calculated as the mean RMS amplitude of the response within the time window. MOC inhibition of CEOAEs obtained in Pascals was expressed as normalized (re: baseline CEOAE level) percent change in CEOAE level (ΔOAEn).

Test for MEMR

In addition to recruiting participants only with high enough ARTs (>70 dB HL), click levels were probed offline for deviations in level during elicitor presentations (re: elicitor-off condition). This test is based on the hypothesis that a significant MEMR would consistently increase probe-tip stimulus levels. This is because, MEMR activation will stiffen the ossicular chain and retract the tympanic membrane, resulting in increased reflection of stimulus energy back to the ear-canal. A cut-off value of 1.4% (0.12 dB) increase in stimulus level during elicitor-on condition compared to elicitor-off condition was suggested as an indication of MEMR activation (Abdala, Dhar, Ahmadi, & Luo, 2014; Abdala, Mishra, & Garinis, 2013).

To test for such large changes in level, RMS levels of the ear-canal recorded stimulus in a time-window near the first trough of the recorded click waveform (125 μs) across all elicitor conditions for every participant were obtained. Individual and mean data of this analysis are plotted in Figure 6-2, which clearly shows that the deviations in stimulus level do not exceed $\pm$0.075 dB. Deviations observed here are very small, and are seen in both directions, i.e., increase and decrease in level. A level reduction would not be expected if MEMR were to act on the stimulus (Abdala et al., 2013).

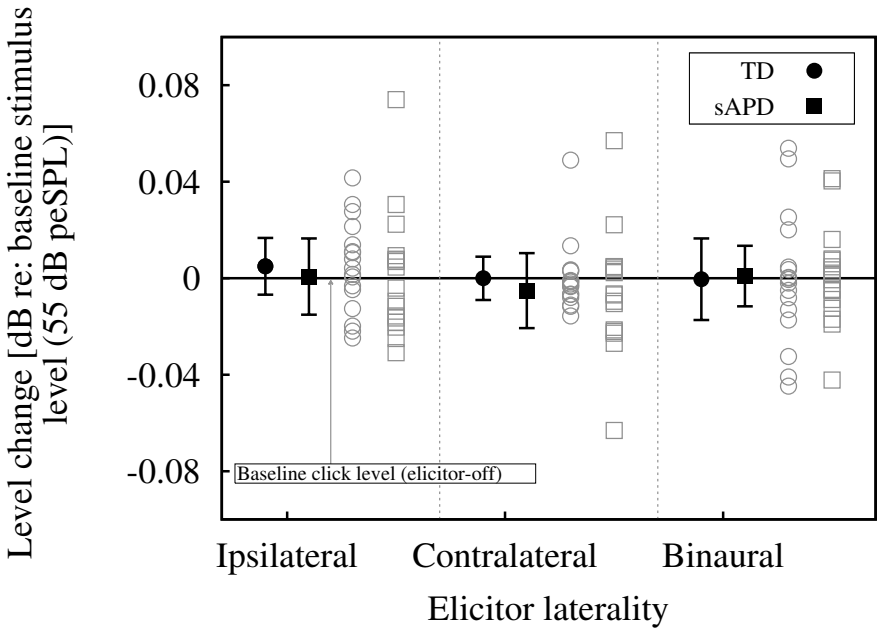

Figure 6-2: Results of MEMR test. Laterality of stimulus presentation is represented on the x-axis, and change in stimulus level with reference to baseline elicitor-off condition (dB) on the y-axis. Black straight line at 0 dB represents normalized baseline stimulus level (in elicitor-off condition). Change in level from baseline is plotted for every elicitor condition. Black filled symbols are group mean with their corresponding 95% confidence intervals represented by error bars. Grey unfilled symbols are individual means of RMS amplitude near the stimulus trough. Circles represent TD and boxes represent sAPD.

Further, one-way repeated measures analysis of variance (RM-ANOVA) was conducted to test for effect of MOC elicitor laterality. If there was an effect of MEMR, a

larger reduction in stimulus level in the binaural elicitor condition would be expected, compared to the two monaural lateralities, due to increased stimulus energy resulting from binaural summation. However, results show no effect of MOC elicitor laterality ($F[2, 68] = 0.26$, $p = 0.74$), suggesting that the observed changes in stimulus levels are not due to MEMR. These changes probably arise due to random fluctuations in background noise. Therefore, any CEOAE level reduction reported in this study is likely only due to MOC activation, rather than MEMR.

6.2.3 Binaural Re-synthesis Test (BR)

BR test was carried out with a two channel clinical audiometer (GSI-61, Grason-Stadler Inc., MN) at 25 dB above participant's thresholds, i.e., 25 dB sensation level (SL). Hearing thresholds at 0.5 and 1 kHz were used to set presentation levels for low- and high-pass channels, respectively, as per Ivey (1969). The audiometer's VU meter was adjusted to zero using a calibration tone prior to testing every participant. Stereo speech stimulus was routed through two channels of the audiometer from a JVC CD player (Model: XL-Z232) and delivered to the ear-canal by two ER-3A (Etymotic Research, IL) insert receivers. Children sat in a double walled sound treated booth (Eckel Industries, ON), and were instructed to repeat the words they heard. The experimenter in the observation room listened to children's responses through the audiometer's talk-back option, and judged if the responses were correct or wrong. There were 20 words for each ear and separate ear scores (% correct) were obtained prior to averaging right and left ear scores to obtain a composite score.

6.2.4 CEOAE data inclusion criteria

For data to be considered for statistical analyses the following criteria had to be satisfied: (1) a correlation coefficient of 0.85 or higher between the two response buffers, (2) <10% epoch rejection, (3) minimum SNR of 10 dB, and (4) no MEMR

activation. Based on the inclusion criteria, four participants from the TD group and nine participants from the sAPD group were rejected from the MOC inhibition study due to poor SNR. Two children did not undergo the BR test due to time constraints, therefore there were 45 participants in analysis of BR.

6.3 Results

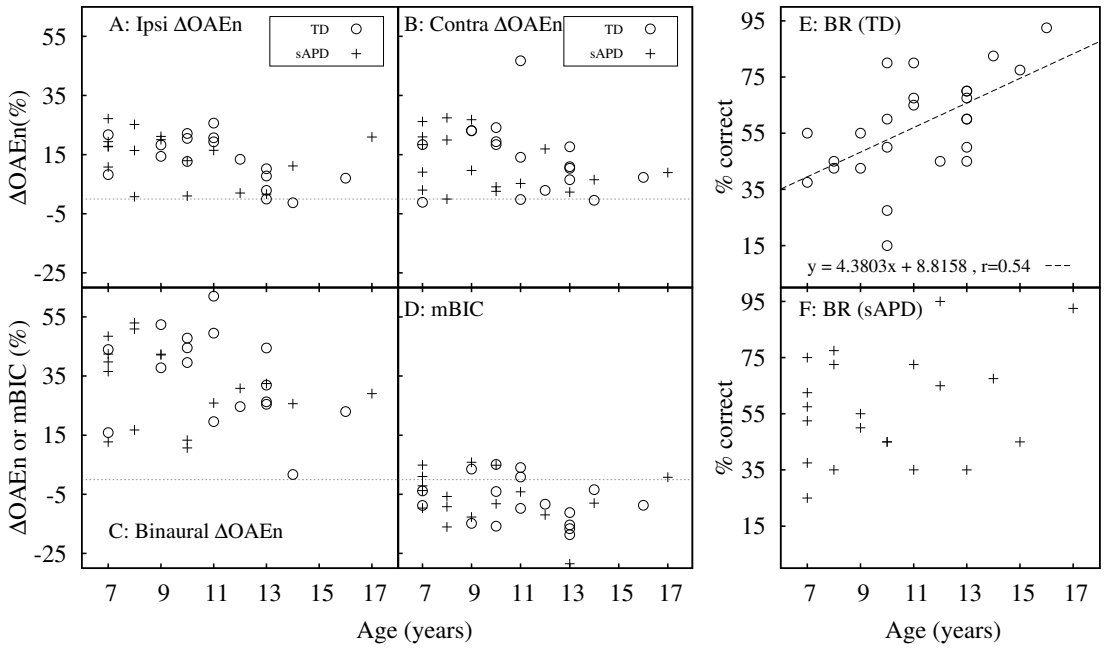

Figure 6-3: All obtained measures are plotted as a function of age for both TD (circles) and sAPD (pluses) groups. In all panels (A-F), x-axis represents age in years, and in panels A-C y-axis represents normalized MOC inhibition (ΔOAEn), and mBIC(%) in panel D. Dotted grey lines are drawn in figures A-C to indicate zero, or no change in CEOAE level due to MOC activation. Dotted grey line in figure D indicate zero mBIC. In panels E and F, Y-axis represents % correct response in the BR test. Significant effect of age for BR in TD is depicted as linear line fit to data in sub-plot E, and its corresponding equation and r is presented at the bottom of the sub-plot. Sub-plot F represents BR as a function of age for sAPD which does not show a significant age trend.

Regression analysis with age as independent variables and ΔOAEn (all elicitor lateralities) and mBIC as dependent variables, did not show any systematic effect of

age within groups (Figure 6-3A-D). However, average ([right ear + left ear]/2) BR scores improved significantly as a function of age in the TD group ($r = 0.54$, $\beta = 4.04$, $t[18] = 2.78$, $p = 0.012$) as seen in Figure 6-3E. No such trend was present in the sAPD group ($\beta = 2.23$, $t[21] = 1.69$, $p = 0.104$), as seen in Figure 6-3F. Considering there was no significant difference in age between TD and sAPD groups (Mean difference [MD] = 1.54, $CI_{95\%} = \pm 1.55$ years, $t[45] = 2.0$, $p = 0.051$) all further analyses were made with groups as a whole for all measures (ΔOAEn, mBIC and BR). RM-ANOVAs were conducted as appropriate, and are described below with Greenhouse-Geisser corrections where necessary.

6.3.1 MOC inhibition

Raw values and group means for ΔOAEn across all elicitor lateralities are presented in Figure 6-4A. Visual examination of the figure shows considerable overlap in ΔOAEn between the two groups. An RM-ANOVA with elicitor laterality as independent variable and ΔOAEn as dependent variable, showed no group interactions ($F[1.69, 54.20] = 0.63$, $p = 0.509$, $\eta^2_{Partial} = 0.02$), as evident in Figure 6-4A. This suggests that the MOC strength is not different across the two groups, contrary to previous studies (e.g., Muchnik et al., 2004), but in keeping with (e.g., Butler et al., 2011). There was a significant effect of elicitor laterality ($F[1.69, 54.20] = 100.81$, $p<0.001$, $\eta^2_{Partial} = 0.76$), owing to the large binaural ΔOAEn.

Post-hoc tests for data collapsed across groups (after false discover rate (FDR: Benjamini & Hochberg, 1995) corrections) showed a significant difference between binaural ΔOAEn and both ipsilateral (MD= 19.93%, $CI_{95\%} = \pm 4.88\%$, $t[33] = 10.41$, $p<0.001$) and contralateral (MD = 20.42%, $CI_{95\%} = \pm 3.31\%$, $t[33] = 15.85$, $p<0.001$) ΔOAEn. There was no difference between ipsilateral and contralateral ΔOAEn (MD= 0.49%, $CI_{95\%} = \pm 3.32\%$, $t[33] = 0.30$, $p = 0.763$), consistent with findings of

other studies that show similar MOC strengths between ipsilateral and contralateral MOC activations (Berlin, Hood, Hurley, Wen, & Kemp, 1995; Lilaonitkul & Guinan, 2009a, 2009b).

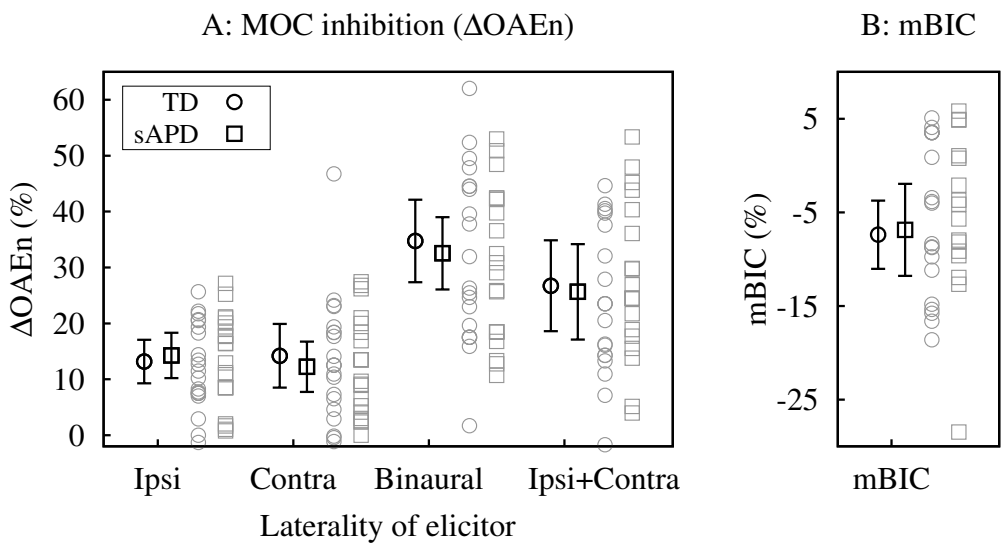

Figure 6-4: In both panels, A and B, symbols in black are normalized mean inhibition (%) across different lateralities plotted on the x-axis. Corresponding grey symbols are individual MOC inhibition data. Circles represent TD and boxes represent sAPD. y-axis in panel A is normalized mean inhibition (%) and in panel B is mBIC (%). Error bars represent 95% confidence interval around the mean.

Independent sample t-test showed no significant difference in mBIC between the two groups (MD= -0.51%, $CI_{95\%} = \pm 6.36\%$, $t[32] = -0.16$, $p = 0.871$), as evident in Figure 6-4B. Lack of difference between groups for mBIC is contrary to eBIC studies that show reduced binaural interaction in children with listening difficulties (Delb et al., 2003; Gopal & Pierel, 1999).

To elucidate if ΔOAEn varies temporally between groups, two temporal analyses were performed. The first temporal analysis is a within-epoch analysis, where the CEOAE time-waveform was separated into six 2.5 ms long sequential time-windows

(5-7.5 ms, 7.5-10 ms, 10-12.5 ms, 12.5-15 ms, 15-17.5 ms, 17.5-20 ms) for all elicitor conditions (including elicitor-off).

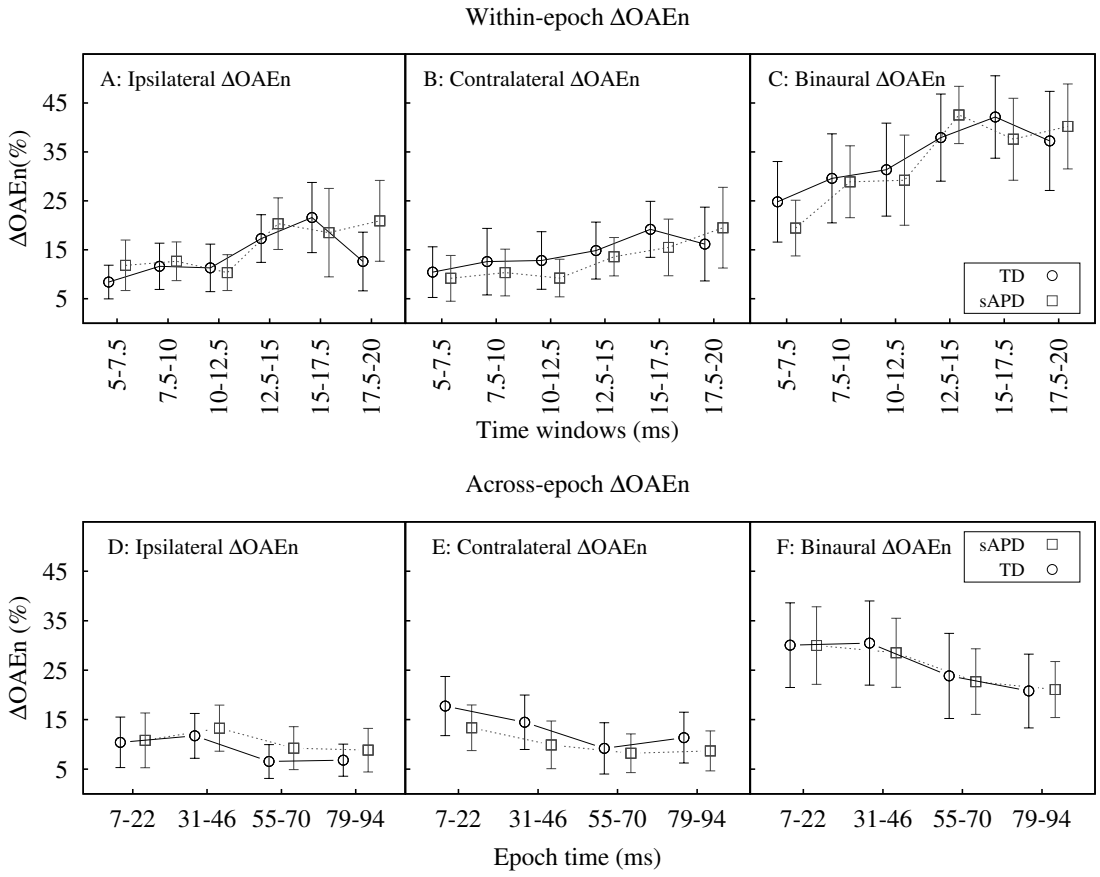

Figure 6-5: Analysis of ΔOAEn across different time scales. Within-epoch analysis is shown in the top row; panels A, B, and C represent ipsilateral, contralateral and binaural elicitor conditions, respectively. Mean ΔOAEn obtained in successive 2.5 ms temporal-bins (X-axis) are plotted for both TD (circles) and sAPD (squares) with ΔOAEn on the Y-axis. Across-epoch analysis is shown in the bottom row; panels D, E, and F represent ipsilateral, contralateral and binaural elicitor conditions, respectively. Mean ΔOAEn (for the entire epoch duration 5-20 ms) obtained in four successive epochs following elicitor cessation is plotted for both TD (circles) and sAPD (squares). In the bottom panels, time on X-axis also includes the 2 ms silent period following elicitor cessation (see Figure 6-1). Error bars represent 95% confidence interval around the mean.

Individual ΔOAEn were then calculated for each of the six time-windows in the same manner as the original ΔOAEn, with the corresponding elicitor-off time-windows as reference. Mean ΔOAEn across time-windows are plotted in Figure 6-5A for both groups separately.

RM-ANOVA with time, elicitor-laterality and group as independent variables and ΔOAEn as dependent variable did not show any significant group interactions, consistent with original ΔOAEn analysis above: elicitor X group interaction (F[2,64] = 1.06, p = 0.354, $\eta^2_{Partial}$ = 0.03), time X group (F[3.76,120.39] = 1.69, p = 0.159, $\eta^2_{Partial}$ = 0.05) and time X elicitor X group (F[5.63,180.02] = 0.71, p = 0.714, $\eta^2_{Partial}$ = 0.02). There was however a significant effect of elicitor (F[2,64] = 95.71, p<0.001, $\eta^2_{Partial}$ = 0.75), owing to larger binaural ΔOAEn. Interestingly, there was a significant interaction between time X elicitor (F[5.63,180.02] = 3.97, p = 0.001, $\eta^2_{Partial}$ = 0.11). This interaction was followed up with post-hoc tests, results are tabulated in Appendix B. Figure 6-5 and post-hoc tests suggest that MOC inhibition increases with time, substantially beyond 10 ms for the binaural elicitor. For both monaural elicitors, the increase in inhibition is not as pronounced.

The second temporal analysis, shown in bottom row of Figure 6-5, is an across-epoch analysis; here, CEOAE levels were obtained for each average epoch (from the train of four average epochs) separately for every elicitor. ΔOAEn was then calculated using the corresponding elicitor-off epoch from the train. This analysis provided data on how MOC inhibition decayed over time, i.e., ΔOAEn from 7-22 ms, 31-46 ms, 55-70 ms, and 79-94 ms after the elicitor had been switched off. Note that the CEOAE recording window is 5-20 ms, however, this temporal analysis takes into consideration the 2 ms gap between elicitor cessation and first click presentation, therefore the analysis time starts at 7 ms, not 5 ms.

In the same fashion as within-epoch temporal analysis, an RM-ANOVA with time, elicitor and group as independent variables and ΔOAEn as dependent variable did not show any significant group interactions: elicitor X group interaction (F[2,64] = 1.32, p = 0.273, $\eta^2_{Partial}$ = 0.04), time X group (F[2.41,77.26] = 0.36, p = 0.783, $\eta^2_{Partial}$ = 0.01) and no 3-way time X elicitor X group (F[4.08, 130.82] = 0.32, p = 0.928, $\eta^2_{Partial}$ = 0.01). There was a significant effect of elicitor (F[2,64] = 70.24, p<0.001, $\eta^2_{Partial}$ = 0.69), and a significant interaction between time X elicitor (F[4.08,130.82] = 3.45, p = 0.01, $\eta^2_{Partial}$ = 0.10). Results of post-hoc tests are tabulated in Appendix C. These results demonstrate decay of MOC inhibition over time. Considering no group differences were found in both additional temporal ΔOAEn analyses, no further analyses were performed to explore rise and decay times of the MOC.

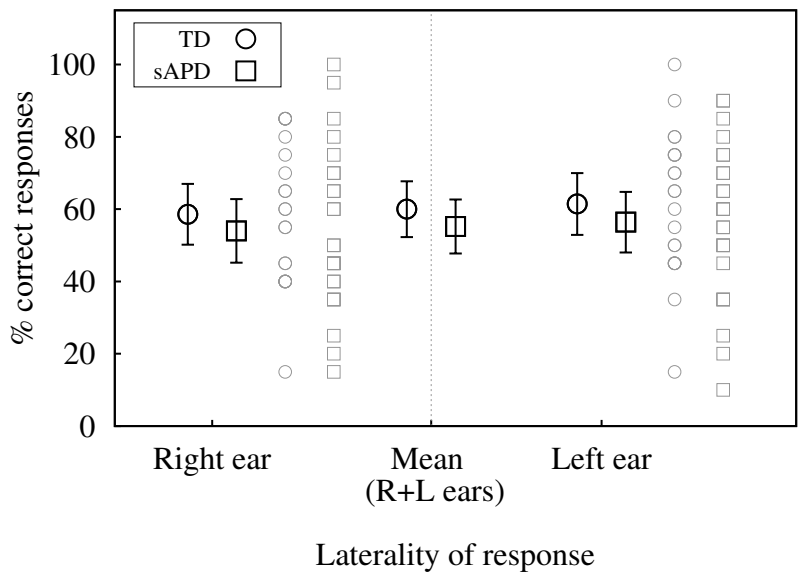

Figure 6-6: Mean scores from the binaural re-synthesis test are plotted as function of laterality of stimulus (ear with low-pass stimulus) presentation. Symbols in black are means with their corresponding 95% confidence intervals represented by error bars. Mean of right and left ear scores are presented at the center of the figure. Grey symbols are individual data. Circles represent TD group and squares represent sAPD group.

6.3.2 Binaural Re-synthesis

Scores obtained for BR (mean of left and right ears) in the TD group (Mean = 60%, SD = 18.01%; right ear: 58.5%; left ear: 61.4%) were not statistically different from the sAPD group (Mean = 55.2%, SD = 19.10%; right ear: 54%; left ear: 56.4%) in an independent-samples t-test ($t[43] = 0.71$, $p = 0.479$). Means and SDs of BR scores for both groups are plotted in Figure 6-6. BR scores of TD group are consistent with Roush and Tait (1984), whose control group scores were 58.5±9.1%. However, their experimental group ('poor listeners') performed worse (38.6±11.8%) than the sAPD group in the current study.

6.4 Discussion

6.4.1 MOC inhibition of OAEs

The current study was undertaken to investigate ipsilateral, contralateral and binaural MOC inhibition of CEOAE in children with listening difficulties, and explore an MOC equivalent of the binaural interaction component. Contrary to previous studies (Garinis et al., 2008; Muchnik et al., 2004; Yalçinkaya, Yilmaz, & Muluk, 2010) that show reduced MOC inhibition in children with listening difficulties, the present results show no difference in ΔOAEn between the two groups. However, these findings are consistent with studies that show no difference in MOC inhibition between TD and sAPD groups (Abdelrazeq, 2014; Burguetti & Carvallo, 2008; Butler et al., 2011; Clarke, Ahmmed, Parker, & Adams, 2006; Veuillet, Magnan, Ecalle, Thai-Van, & Collet, 2007). Several factors could have led to the difference between the present and previous studies that show significant differences. We will first consider methodological differences between previous OAE studies and the present study. A forward masking MOC paradigm was used in the present study to evoke the MOC

response. All previous studies have used a simultaneous elicitor paradigm. However, if the hypothesis that MOC function is weaker in children with listening difficulties is true, a weaker MOC function should reveal itself in any type of MOC stimulation, simultaneous or forward masked. One exception could be if MOC inhibition of OAEs decayed over time more quickly in children with sAPD compared to TD. However, as evidenced in Figure 6-5B, MOC decay across time is near identical for the two groups. Therefore, differences in MOC activation (forward masked vs. simultaneous activation) should not cause differences in MOC inhibition of OAEs across groups.

Secondly, previous studies that report a significant difference between APD and TD have used high click presentation levels (60 to 80 dB peSPL) and faster click presentation rates (50 Hz). From Veuillet et al. (1991) and Guinan, Backus, Lilaonitkul, and Aharonson (2003) it is clear that clicks presented at high levels and faster rates evoke ipsilateral MOC activity, and possibly MEMR. Both Muchnik et al. (2004) and Sanches and Carvallo (2006) did not control for MEMR in their respective studies. Muchnik et al. (2004) reported that normal contralateral acoustic reflex was one of their criterion for including children in their study, but did not mention any cut-off values. Recent studies have shown that MEMR can be evoked at much lower levels, in normal hearing individuals, than acoustic reflex thresholds obtained from a clinical immitance meter (Goodman, Mertes, Lewis, & Weissbeck, 2013; Guinan et al., 2003; Schairer, Ellison, Fitzpatrick, & Keefe, 2007; Zhao & Dhar, 2009). Further, children with suspected APD have been reported to have elevated or absent MEMR, which has been thought to be part of their deficits in neural integrity (Allen & Allan, 2014). Collectively, elevated MEMR in sAPD children, and use of a stimulus that can potentially evoke MEMR in the TD group could lead to an apparent increase in MOC inhibition in the TD group. This may be interpreted as reduced MOC functioning in the APD group. In the present study, with a combination of

low click levels (55 dB peSPL) and with only four clicks presented in sequence at a slower rate of 41.67 Hz, MEMR was carefully controlled. Further, additional tests provide confidence that MEMR was not activated in the present study. This evidence supports the notion that MEMR mediated reduction in OAE level in the TD group, but not in the study group, cannot be ruled out in previous studies that report differences in MOC inhibition for children with listening difficulties and their controls.

Thirdly, differences in inclusion criteria used to group children as sAPD and TD between the studies may have potentially led to the differences between the present study and previous studies that show group differences. Muchnik et al. (2004) only included children with a diagnosis of APD in their APD group. Their APD diagnosis was based on Bellis (1996), who suggests positive APD diagnosis if a child fails in one or more central auditory processing tests. Muchnik et al. (2004) used a competing sentences test, a speech-in-noise test, a gap detection test, binaural masking level difference, and auditory brainstem response. Sanches and Carvallo (2006) segregated children into the APD group if they scored <68% in a speech-in-noise test and scored <85% on SSW test. These tests are similar to the test battery used in the present study. Although ASHA (2005) guidelines for diagnosis of APD were followed in the present study, they are not different from Bellis (1996). However, all children that presented with listening difficulties were included in the sAPD group in the present study, irrespective of their diagnosis as APD or non-APD, unlike both Muchnik et al. (2004) and Sanches and Carvallo (2006). It is possible that inclusion of non-APD children together with APD children in the present study might have reduced any contrasts between the sAPD and TD groups. To test if non-APD children had larger MOC inhibition than children diagnosed as APD, additional analyses were performed where APD ($n = 10$) and non-APD ($n = 7$) were separated into two groups and their MOC inhibition were compared using independent sample t-tests. Results showed

no significant difference in MOC inhibition for ipsilateral (t[15]= -0.14, p = 0.891), contralateral (t[15]= -0.17, p = 0.867) and binaural MOC (t[15]= -0.66, p = 0.515) lateralities between APD and non-APD children. This suggests that inclusion of non-APD children may not have improved MOC inhibition of the sAPD group. It is also likely that diagnosing APD using current behavioral tests and procedures may not be adequate to identify subtle deficits in auditory physiology. This is either because of the variability in auditory processing deficits within the group, or mis-diagnosis of children with problems in non-auditory modalities as APD using the current test battery (Allen & Allan, 2014). By including children diagnosed as APD and as non-APD together in the sAPD group, we attempted to mitigate the limitations of the behavioral test battery. However, segregating children according to their auditory deficits, obtained either using behavioral or physiological measures, may provide a better avenue for studying MOC strengths in different auditory processing problems.

In the present study, similarity between the two groups for all three lateralities suggests that MOC function is similar across the two groups, at least when measured using CEOAEs. Despite the difference in the type of OAE used, the present results are consistent with Butler et al. (2011) and Abdelrazeq (2014), both these studies used DPOAEs. DPOAEs measured in the ear canal are a complex mixture of OAEs generated from two different places, corresponding to two different generation mechanisms (coherent linear reflection and non-linear distortion) on the the basilar membrane (Shera & Guinan, 1999). CEOAEs on the other hand are thought to be generated mainly by coherent linear reflection (Kalluri & Shera, 2007), although some contributions to CEOAE from distortion components do exist (Withnell, Dhar, & Thomsen, 2005; Yates & Withnell, 1999). Butler et al. (2011) discussed how differences between their results and those of Muchnik et al. (2004) and Sanches and Carvallo (2006) could arise from differences in the type of OAE used to study

MOC inhibition. Results from the present study, and that of Abdelrazeq (2014) who separated DPOAE components in his study, suggest that this may not be the case, considering results from the present study using CEOAEs also do not show group differences in MOC inhibition of OAEs. However, further studies that record different OAE types in a repeated measures design are required to resolve the use of different OAEs in comparing MOC inhibition across two study groups, such as sAPD and TD.

In conclusion, MOC inhibition of OAEs, across the three lateralities appear to be similar in sAPD and TD groups, at least when measured using CEOAEs. Methodological caveats may likely explain the difference in results between the present study and previous studies that show significant group differences in MOC inhibition between children with and without APD.

6.4.2 Binaural interaction and mBIC

A secondary aim of this study was to better understand binaural interaction (mBIC) at the level of MOC, and explore any differences in mBIC between the two groups. Results indicate that binaural facilitation is predominant in both groups, consistent with similar ΔOAEn across groups. Although several studies have measured both monaural and binaural MOC inhibition of OAEs, a binaural interaction has not been explicitly studied. Backus and Guinan (2006) briefly mentioned that two out of three participants in their study showed binaural facilitation, while one participant showed binaural inhibition$_A$. The current study thus presents novel findings on binaural interaction at the level of the MOC. Therefore, to understand mBIC findings, we will compare it with eBIC studies in the APD realm.

Results of mBIC in the present study are different from results of eBIC studies in two ways; (1) mBIC predominantly displays binaural facilitation despite large

variability, whereas eBIC shows inhibition$_A$ (Dobie & Norton, 1980; McPherson & Starr, 1993; Wada & Starr, 1989), (2) no difference between sAPD and TD groups in mBIC, whereas eBIC shows significant differences (Delb et al., 2003; Gopal & Pierel, 1999). Several reasons could lead to differences between the two measures. Firstly, mBIC captures efferent activity that originates at the level of lower brainstem, whereas eBIC can be generated from anywhere in the auditory system from brainstem to cortex (McPherson & Starr, 1993; Wada & Starr, 1989). Further, McPherson and Starr (1993) showed that eBIC increases as its generation site moves rostrally. If the efferents are governed by the same gradient in binaural inhibition$_A$ that applies to eBIC, the position of MOC neurons (Liberman, 1988; Warr, 1992) towards the caudal end of this gradient would predict minimal inhibition or even facilitation.

Secondly, physiological studies show that the response of an ipsilateral MOC neuron is typically facilitated by contralateral acoustic stimulation (Liberman, 1988). Brown et al. (1998) extensively studied single neuron properties of the MOC to binaural stimulation, and concluded that the response of most MOC neurons are facilitated by binaural stimulation. This could lead to negative mBIC. In contrast, afferent responses from the medial superior olive (MSO) and lateral superior olive (LSO) show inhibition to binaural stimulation (Covey, Vater, & Casseday, 1991; Grothe & Sanes, 1993). Covey et al. (1991) reported that output of LSO neurons to ipsilateral stimulation were completely suppressed when a contralateral stimulus of the same level was introduced. In the MSO however, the output was not completely suppressed even at high contralateral stimulus level, but suppression of responses was predominant. Also, inhibition$_A$ of binaural afferent responses are thought to essential for sound localization (Covey et al., 1991; Yin & Chan, 1990). It thus appears that the afferent auditory system produces positive BICs, arising from inhibition$_A$ of binaural responses, in contrast to the MOC, which facilitates binaural responses, both

for different reasons. Facilitation of binaural responses by the MOC may be beneficial for inhibition of cochlear amplification in a manner that is adaptive to input sound levels, especially for loud sounds where it offers protection against haircell damage (Rajan & Johnstone, 1988). Thus, in addition to the obvious afferent/efferent differences between eBIC and mBIC, respectively, these BICs reflect fundamentally different auditory phenomena that serve entirely different purposes in the auditory system. Further physiological studies that closely compare and contrast these two BICs may provide further insights into their characteristics.

One reason for the lack of difference in mBIC between TD and sAPD groups could be that mBIC simply reflects the similarity in ΔOAEn across lateralities. Further, results of mBIC corroborates equal performance in BR between the two groups. Although no attempts were made to correlate these measures, their outcome suggests that binaural interaction in the sAPD and TD groups may be similar. This result is inconsistent with Roush and Tait (1984) who reported poor BR scores in language-learning disabled children with listening difficulties. BR scores in the TD group are consistent with those of Roush and Tait (1984), but their study group performed much poorer. One possible reason for the lack of difference in BR at a group level could be due to the difference in processing difficulties experienced by each child in the sAPD group. Children in the sAPD group failed almost equally across the five tests in the APD test battery (SSW, PPT, GDT, and WIC), but fewer children failed in the frequency discrimination test. This variability in auditory processing skills suggests a lack of consistency in binaural processing deficits among sAPD. Allen and Allan (2014) also reported that no one objective or behavioral test was abnormal in all children in their APD or non-APD group, and objective measures did not always correlate with behavioral test outcomes. Allen and Allan (2014) suggested that basing APD diagnosis on behavioral tests alone may misdiagnose children as APD if they

had language or attention related problems.

On the other hand, behavioral tests alone may also miss children with genuine auditory deficits who compensate for their auditory problems with superior language and attention skills. Perhaps, children in the sAPD group in the present study fall in the former category, where their auditory processing may be on par with TD children but other non-auditory factors play a predominant role in their listening problems. Such children, at least at a group level, may not be different in either behavioral (BR) or physiological measures (mBIC) from the TD group. One way to filter-out such children is to study children with known behavioral and physiological (e.g., in ABR, elevated ART) deficits. It appears that, to better understand relationships between MOC function and APD, specific processing deficiencies must be studied individually. Comparing APD as a group with TD on physiological measures such as MOC inhibition of OAEs comes with large variability due to children with varied processing issues. For example, to reduce this variability, mBIC could be studied specifically in children who fail binaural masking level difference (BMLD), considering BMLD is a binaural interaction test.

Another reason for lack of difference in BR scores between groups could be due to the large variability of scores in both groups. In contrast, SDs for BR scores in Roush and Tait (1984) were almost half of SDs obtained in the present study. Increased variability could have stemmed from the larger age range included in the present study, 7-17 years, compared to 6-12 years in Roush and Tait (1984). Further, variability may also arise due to improvement in BR scores with age in both groups, although this trend was not statistically significant in the sAPD group. The significant correlation between BR scores and age suggests that binaural interaction measured using the BR test may not be mature in this age range, and continues to develop until

late teenage years. This hypothesis is consistent with maturation of other complex binaural processes such as the precedence effect (Litovsky, 1997). However, this relationship should be interpreted with caution because a limited number of children represent different age groups in the present study.

6.5 Conclusion

The present study aimed to elucidate ipsilateral, contralateral and binaural MOC functioning, and explore binaural interaction at the level of the MOC in children with listening difficulties (sAPD). Results suggest that children in the sAPD group do not differ from the TD group in their MOC strength in all three lateralities. This is consistent with Butler et al. (2011) but is contrary to the findings of Muchnik et al. (2004) and Sanches and Carvallo (2006). Methodological differences across studies could have possibly led to differences in findings across studies. Results of mBIC and BR corroborate with the lack of difference in MOC inhibition of CEOAE between the two groups. The predominantly negative mBIC compared to positive eBICs may be explained based on their generation sites, and the response properties of neurons in the efferent (MOC) vs. afferent (MSO and LSO) circuitry. Further studies that separate children based on their specific auditory processing issue are required to explore relationships between MOC function and specific auditory processing deficiencies.

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Chapter 7

Contralateral Inhibition of Multiple Otoacoustic Emission Types in Children with Suspected Auditory Processing Disorder

7.1 Introduction

Cortical feedback networks fine tune bottom-up signal encoding, and control overall gain in the auditory system (Khalfa et al., 2001; León, Elgueda, Silva, Hamame, & Delano, 2012; Perrot et al., 2006; Robinson & McAlpine, 2009; Winer, 2006; Xiao & Suga, 2002). The medial olivocochlear system (MOC) from the periolivary group of neurons form one of the final legs in this network by contacting cochlear outer haircells (OHCs) directly. MOC neurons in the brainstem receive inputs from both ascending (Liberman, 1988a) and descending (Mulders & Robertson, 2000) auditory fibers. Although their projections to the cochlea are tonotopic, a single MOC neuron can receive ascending inputs of multiple frequencies, and they are particularly sensitive to noise (Liberman, 1988a). In the cochlea, a single OHC could be supplied by as many as 8-10 MOC synapses, and a single MOC axon can innervate multiple OHCs spanning up to one octave (Liberman & Brown, 1986). The MOC input to OHCs is cholinergic, therefore acoustic or electric stimulation of the MOC reduces

the putative cochlear amplification process (Guinan, 2006). Considering otoacoustic emissions (OAEs) are a direct byproduct of cochlear amplification, MOC inhibitory action is typically assayed using OAEs (Collet et al., 1990; Guinan, 2006). Inhibition of OHC activity is thought to restore the dynamic range of afferent fibers by reducing cochlear amplification for steady-state noise, while allowing encoding of transient stimuli (Kawase, Delgutte, & Liberman, 1993; Winslow & Sachs, 1988). This 'unmasking' is thought to improve speech perception in noise.

Understanding anatomic underpinnings of speech-in-noise difficulties is particularly relevant in auditory processing disorder (APD). This is because, difficulty understanding speech in noise despite clinically normal hearing is the prime complaint of individuals with APD. APD is broadly defined as "difficulties in the perceptual processing of auditory information in the central nervous system and the neurobiological activity that underlies the processing"(American Academy of Audiology [AAA], 2010). Despite several decades of research, there is no clear consensus on the diagnostic process of APD, nor the definition of APD itself. Typically, behavioral tests are used as part of a test battery assessment (e.g., dichotic listening tests such as Staggered Spondaic Word Test) in diagnosis of APD. However, most behavioral tests for APD are criticized for tapping non-auditory processes that may influence test results and limit them from providing a true representation of the underlying deficit (Allen & Allan, 2014; Cacace & McFarland, 2005; Moore, Ferguson, Edmondson-Jones, Ratib, & Riley, 2010).

Recommendations have been made to include objective tests that can identify a breakdown in processing (AAA, 2010; Allen & Allan, 2014; American Speech-Language-Hearing Association [ASHA], 2005; Canadian Interorganizational Steering Group for Speech-Language Pathology and Audiology [CISG], 2012). Although

studies have identified abnormalities in brainstem afferent signal encoding, profiled using objective measures (e.g., Allen & Allan, 2014; Gopal & Pierel, 1999; Hornickel & Kraus, 2013), an objective diagnostic tool for APD does not exist yet. Some studies have used the aforementioned unmasking property of the MOC to investigate potential abnormalities in the efferent pathway in individuals with listening problems, especially in noise. Thus far, MOC function in individuals with listening difficulties associated with different disorders has been studied: APD (Burguetti & Carvallo, 2008; Butler, Purcell, & Allen, 2011; Muchnik et al., 2004; Sanches & Carvallo, 2006; Yalçinkaya, Yilmaz, & Muluk, 2010), specific language impairment (Clarke, Ahmmed, Parker, & Adams, 2006), learning/reading disabilities (Garinis, Glattke, & Cone-Wesson, 2008; Veuillet, Magnan, Ecalle, Thai-Van, & Collet, 2007), auditory dyssynchrony (Berlin, Hood, Cecola, Jackson, & Szabo, 1993) and selective mutism (Bar-Haim et al., 2004). While some studies show significantly reduced MOC inhibition in their study group compared to control group (Garinis et al., 2008; Muchnik et al., 2004; Sanches & Carvallo, 2006; Yalçinkaya et al., 2010), others do not (Abdelrazeq, 2014; Burguetti & Carvallo, 2008; Butler et al., 2011; Clarke et al., 2006; Veuillet et al., 2007). However, the trend is towards lower MOC inhibition in study groups of investigations that do not show statistically significant group differences.

If MOC function is indeed affected in APD, MOC assays may serve as a diagnostic tool in the APD test battery. Considering MOC is amenable to training (de Boer & Thornton, 2008; Irving, Moore, Liberman, & Sumner, 2011; Veuillet et al., 2007), targeted regimens might be established to strengthen efferent networks in individuals with APD, to help their speech perception difficulties (Veuillet et al., 2007). Currently however, there is no clear consensus on MOC function in children with APD. Therefore, it is paramount to elucidate if MOC function in individuals

with APD is indeed affected or not. First, differences between studies that report contrasting results on MOC function in APD must be gleaned to better understand the reasons for such contrasting findings. Contrasting findings between the above mentioned APD-MOC studies probably arise due to methodological differences.

Many previous studies have not addressed methodological caveats critical for MOC assays that can potentially lead to incorrect interpretation of results. Recent studies (Guinan, Backus, Lilaonitkul, & Aharonson, 2003; Zhao & Dhar, 2009) have shown that the middle ear muscle reflex (MEMR) can be evoked at levels much lower than acoustic reflex thresholds (ARTs), and can thus inflate true MOC effects. The most common reasons that lead to unwanted activation of MEMR are high stimulus presentation level (Guinan et al., 2003) and high MOC elicitor level (>60 dB SPL; Guinan et al., 2003; Veuillet, Collet, & Duclaux, 1991). Stimuli (clicks) presented at levels 60 dB peSPL and above have been shown to evoke MOC activity, and higher levels could even evoke MEMR (Guinan et al., 2003). While some studies have adhered to using relatively low level stimuli (Butler et al., 2011; Clarke et al., 2006; Garinis et al., 2008; Veuillet et al., 2007) others have used click stimuli that are at least 80 dB peSPL in amplitude (Muchnik et al., 2004; Sanches & Carvallo, 2006; Yalçinkaya et al., 2010). In addition to click and elicitor levels, rapid click presentation rates influence contralateral MOC inhibition by evoking ipsilateral and binaural MOC activity. The observed OAE inhibition will thus be complicated due to activation of ipsilateral, contralateral and binaural MOC, often with large variability across samples. With the exception of studies that assayed MOC activity using distortion product OAEs (DPOAE; Abdelrazeq, 2014; Butler et al., 2011), most click evoked OAE (CEOAE) studies have either used the standard 50 Hz click rate, or did not report this parameter.

Further, a 3 dB signal-to-noise ratio (SNR) criteria is typically used in clinical

settings to reliably differentiate OAE from the noise floor. However, Mishra and Lutman (2013) suggested that at least 6 dB SNR is required for MOC assays to avoid the noise floor from influencing OAE levels. Other investigators recommend SNRs of 9 dB or higher for MOC assays (Francis & Guinan, 2010; Goodman, Mertes, Lewis, & Weissbeck, 2013). Most APD-MOC studies mentioned above have either used a 3 dB SNR cut-off, or have not mentioned any SNR criterion. Poor SNR or high noise levels can modulate OAE level, and difference in noise levels across MOC elicitor-on and -off conditions may further complicate interpretation of the observed MOC inhibition of OAEs.

Another caveat that can affect MOC assays is the systematic change in stimulus level across measurement duration due to probe drifts. Goodman et al. (2013) reported that unless probe-drifts in stimulus level are accounted for, they can cause spurious changes in MOC inhibition of OAEs. Past APD-MOC studies have typically used continuous presentation of the elicitor, as opposed to an interleaved elicitor-on and -off strategy. Obtaining MOC inhibition of OAEs from measurements that are made far apart in time can lead to an artificial decrease in OAE level in later conditions due to probe-drifts. Such changes in level may be mistaken for reduction in OAE level due to MOC activation (Goodman et al., 2013). Interleaving elicitor-on and -off conditions in short durations may minimize such caveats, or completely eliminate them. Signal processing methods such as 'de-trending' can remove probe-drifts, but only one study to date has used this method (Goodman et al., 2013).

The CEOAE is readily available to clinicians, and given several frequencies can be studied at once, it appears logical to use them to assay the MOC. With the exception of two studies (Abdelrazeq, 2014; Butler et al., 2011), all other APD-MOC studies have used CEOAEs to assay MOC activity in their respective study groups. Due to

the broadband nature of the click stimulus and its rapid presentation method, many of the above mentioned confounds pertain to the use of clicks. On the other hand, while Butler et al. (2011) have used an interleaved elicitor presentation, low stimulus and elicitor levels, and robust noise rejection methods, they did not separate DPOAE components. DPOAEs measured in the ear-canal are complex mixtures of OAE wavelets arising from two different places on the basilar membrane: f_2 frequency place (distortion component) and $2f_1 - f_2$ frequency place (reflection component). This is the result of two different generation mechanisms: non-linear distortion and linear coherent reflection, respectively (Kalluri & Shera, 2001; Shera & Guinan, 1999). Abdala, Mishra, and Williams (2009) reported that the reflection component is inhibited more by the MOC, compared to the distortion component. They suggested that the large level difference typically observed between the two emission types (reflection <distortion) may be responsible for their difference in MOC inhibition. Whatever may be the reason, separating DPOAE components is critical because artificial level enhancements (as opposed to level reduction) may occur due to a different MOC effect on the phase of the two DPOAE components (Abdala et al., 2009; Deeter, Abel, Calandruccio, & Dhar, 2009). Nevertheless, Abdelrazeq (2014) showed that MOC inhibition is not different between children diagnosed as APD and controls, even after separating the two DPOAE components, corroborating results reported by Butler et al. (2011).

Most aforementioned caveats can be addressed with the use of stimulus frequency OAEs (SFOAEs). SFOAEs can be evoked at relatively low stimulus levels (e.g., 40 dB SPL) where the cochlear amplifier is most active, allowing for better visualization of the MOC inhibitory effect (Guinan et al., 2003). SFOAEs are also generated from a narrow region on the basilar membrane by coherent reflection, making them easily interpretable compared to DPOAEs (Shera & Guinan, 1999). Although CEOAEs are

thought to be primarily reflection emissions, they have been shown to contain some non-linear distortion products (Yates & Withnell, 1999). To elucidate MOC function in children with listening difficulties, the present study sought to obtain MOC activity assayed using three types of OAEs in the same individuals: SFOAE, CEOAE, and DPOAE (components unmixed). Steps were taken to avoid methodological caveats discussed earlier. The study asked whether MOC inhibition of OAEs is affected in children with listening difficulties, and is MOC inhibition of OAEs coherent across the three OAE types used?

7.2 Method

7.2.1 Participants

Seventy-two children in the age range 7-17 years, twenty-five typically developing children (TD group, mean age = 11.4±2.7 years, 14 females) and forty-seven children referred to our in-house Audiology clinic with listening problems took part in the study (suspected APD group: sAPD, mean age = 9.6±2.6 years, 9 females). All children had normal middle ear function as determined by clinical tympanometry (GSI-TympStar, Grason-Stadler Inc., MN) and hearing thresholds of 20 dB HL or better at octave intervals between 0.25 and 8 kHz, measured using a clinical audiometer (GSI-61, Grason-Stadler Inc., MN). All children had contralateral acoustic reflex thresholds >70 dB HL for steady state broadband noise (BBN). Children also underwent a screening DPOAE measurement (Integrity v-500, Vivosonic Inc., ON) to confirm the presence of OAEs.

Children in the sAPD group underwent a test battery similar to that used by Allen and Allan (2014) that included three standard clinical tests: the Staggered Spondaic Word Test (SSW; Katz, 1998), Words in Ipsilateral Competition (WIC; Ivey, 1969)

and Pitch Pattern Sequence test (PPS; Pinheiro, 1977), and two psychoacoustic tests that use adaptive procedures developed in-house for use with children: Gap Detection (GD), and Difference Limen for Frequency (DLF). Tests were administered in accordance with their respective manuals and were interpreted according to published age-specific normative data. Of the 47 children in the sAPD group, 32 were diagnosed as having APD based on ASHA (2005) guidelines, i.e., scored 2 standard deviations (SDs) below the normative expectation on at least two tests. Of the 15 children who did not obtain the diagnosis, 11 children failed in one test, and 4 children passed all tests. Of the 15 children who passed all or all-but-one behavioral measures, all had atypical ABR in the form of prolonged peak latencies; prolonged inter-peak latencies; or abnormal wave I-V amplitude ratio. Abnormalities in ABR have been recently reported in children suspected with APD. A recent study (Allen & Allan, 2014) showed that behavioral tests alone may not be adequate in diagnosis of APD, which supports recommendations by professional bodies (e.g., AAA, 2010). Allen and Allan (2014) found several children who passed these behavioral tests had abnormal neural encoding of sound measured using ABR and/or absent/elevated acoustic reflex thresholds. Therefore, children who passed the behavioral test battery but who had abnormal ABR were also included in the study group (sAPD) along with children diagnosed as APD.

Participants sat in a comfortable chair in a double-walled sound attenuated booth (Eckel Industries, ON) and watched a silent closed captioned movie. They were encouraged to relax, and swallow as few times as comfortable. OAEs were recorded from only one ear per participant. The ear being tested was chosen based on DPOAE amplitude obtained during the screening process. Study methods were approved by the Health Sciences Research Ethics Board of Western University, Canada. The nature of the study was explained prior to obtaining written informed assent from every

participant, and informed consent from participants' parent/caregiver. Participants were compensated for their time with gift cards towards books or school supplies.

7.2.2 OAE recording

Signals were played through a digital-to-analog converter (National Instruments 6289 m-series, TX) at a sampling rate of 32 kHz to three separate programmable attenuators (PA5; Tucker-Davis Technologies, FL) that controlled the output signal levels. OAE evoking stimuli (clicks and tones) were always presented in channel-1, with the exception of f_1 in the DPOAE experiment which was presented in channel-2. Both channel-1 and 2 were routed to the ipsilateral ear, as illustrated in Figure 7-1. These signals were power amplified (SA1; Tucker-Davis Technologies, FL) and fed to ER2 transducers (Etymotic Research, IL) connected to an ER-10B+ otoacoustic emission probe system (Etymotic Research, IL) that delivered signals in the ear-canal. A single ER2 insert receiver delivered elicitors in the contralateral ear (contra-channel). All stimuli were calibrated using a Type-2250 sound level meter (Brüel and Kjær, Denmark), and an ear simulator Type-4157 (IEC 711; Brüel and Kjær, Denmark). Responses were recorded using the ER-10B+ probe system with the pre-amplifier gain set at +40 dB. The recorded signal was then fed through a bandpass filter (Frequency Devices Inc., IL; chasis 90IP with a 90PF dual-channel programmable filter card) that filtered responses from 0.4 to 10 kHz and applied a further 20 dB gain. The filtered response was then digitized by an analog-to-digital converter (National Instruments 6289 m-series, TX) which applied another 6 dB of gain prior to conversion. Stimulus delivery and response acquisition were controlled using custom programs developed in LabView (National Instruments, TX), similar to Purcell, Butler, Saunders, and Allen (2008).

7.2.3 Stimuli and response characteristics

All stimuli were digitally generated in Matlab (Mathworks Inc, MA) at a sampling rate of 32 kHz. The temporal order of stimulus presentation for all OAE types is illustrated in different panels in Figure 7-1. Stimulus levels for all OAE types were chosen to obtain the largest OAE while minimizing the possibility of the OAE stimulus evoking the ipsilateral MOC pathway (Guinan et al., 2003; Hood, Berlin, Hurley, Cecola, & Bell, 1996; Schairer, Ellison, Fitzpatrick, & Keefe, 2006; Veuillet et al., 1991) and middle ear muscle reflex (Guinan et al., 2003). All OAE evoking stimuli were presented in an 'epoch', the duration of which varied across the three OAE types. Successive epochs were concatenated to make a 'sweep-block'. The number of epochs in a given sweep-block varied with OAE type, due to the difference in duration of different OAE evoking stimuli. The MOC elicitor remained on for the duration of one sweep-block. Sweep-blocks with and without contralateral MOC elicitors were interleaved with a silent gap: an inter-sweep-block-interval (ISBI) or an inter-sweep-interval (ISI). As seen in Figure 7-1 (for CEOAE and DPOAE measurements), both these interval durations vary across OAE types. This was done to include an integer number of 1.024 s windows in one complete sweep, to match the restrictions of our measurement system. The goal of an ISI was to allow the MOC to revert back to its baseline activity (after MOC activation by the elicitor) before OAE evoking stimuli were presented again. This gap should at least be 200 ms in duration, commensurate with the MOC decay time (Backus & Guinan, 2006). Duration of a sweep-block (across OAE types) was less than 9 s long. Such short duration sweep-blocks were employed, instead of continuous stimulus presentation to ensure that stimulus levels across conditions were not affected by probe-drifts. Specific details of different OAE evoking stimuli are described below.

SFOAE - stimulus

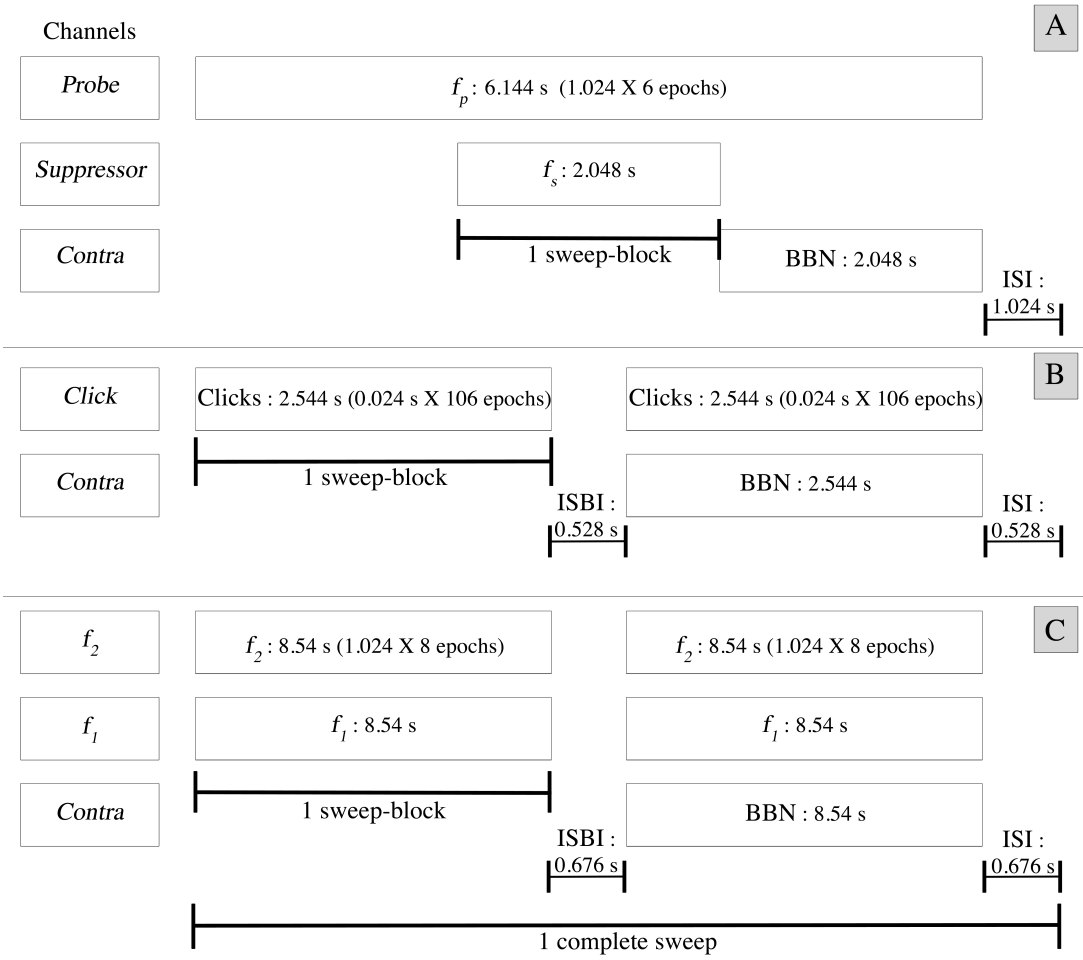

Figure 7-1: Schematic representation and temporal sequence of events for (A) SFOAE, (B) CEOAE, and (C) DPOAE recorded with and without MOC elicitors. Channels indicate separate physical transducers. Duration of each epoch, and sweep-block across OAE types, are mentioned within their respective channels (in rectangular boxes). Note that size of each element in the figure are made disproportionate to their duration to show shorter events clearly.

Probe-tones (f_P) 2.048 s in duration and 40 dB SPL in level, in the frequency range 0.928 to 1.248 kHz at 16 Hz intervals were used to evoke SFOAEs. This frequency region, approximately representing the 1 kHz region, was chosen based on empirical evidence of its pronounced MOC activity (Lilaonitkul & Guinan, 2012;

Zhao & Dhar, 2012). Intra-cochlear suppressor tones (f_S) corresponding to each f_P (where, $f_S = f_P + 16$ Hz) with linear rise/fall ramps of 50 ms duration and 60 dB SPL in level were used according to the suppression method (Brass & Kemp, 1993; Guinan, 1990) to extract SFOAEs using discrete Fourier transforms. Frequencies of all tones were adjusted to have an integer number of cycles in the analysis window. As seen in Figure 7-1A, stimulus epoch duration in the SFOAE experiment was 1.024 s and sweep-blocks were made of two consecutive epochs of the same stimulus. One complete sweep had three sweep-blocks: 1. f_P in isolation, 2. f_P with f_S, and f_P with elicitor in contra-channel (elicitor-on condition). The inter-sweep interval was 1.024 s, and total duration of a sweep was 7.168 s. An in-the-ear calibration of the tones was carried out before every measurement to produce desired SPL in the earcanal. Each frequency sweep was repeated at least five times to obtain reliable SFOAEs. Additional epochs were recorded for every noisy epoch (if RMS amplitude exceeded 0 dB SPL in the 0.5 to 0.9 kHz band), for clipped epochs, or if the SNR was lower than 10 dB.

SFOAE - response extraction

To start, the first and last 128 ms of every response were discarded to remove SFOAE obtained during the raise/fall phase of the elicitor and to avoid transients that may have occurred due to stimulus onset/offset. All epochs were evaluated offline using a discrete Fourier transform to obtain noise metrics in a 20 Hz band just below f_P. Epochs with noise metrics that exceeded the mean plus two SDs were not included in the average response sweep. A vector subtraction of the average ear canal pressure in sweep-blocks one and two yielded the baseline SFOAE (P_{SF}), i.e., SFOAE in elicitor-off condition. Similarly, vector subtraction of sweep-blocks two and three yielded SFOAE after MOC inhibition, i.e., elicitor-on condition. MOC inhibition of SFOAE obtained in Pascals was expressed as normalized (re: baseline SFOAE level) percent

change in SFOAE level (ΔSFn).

CEOAE - stimulus

CEOAE were evoked using unfiltered clicks of 93.75 μs duration, corresponding to four sample points at 32 kHz sampling rate, and were presented at 55 dB peSPL. A single iso-voltage calibration of clicks was performed to set their level using an ear simulator Type-4157 (IEC711; Brüel and Kjær, Denmark). Clicks were presented in epochs that were 24 ms in duration. This translated to a slower than typical (50 Hz) presentation rate of 41.67 Hz. A train of 106 epochs encompassed one sweep-block. As illustrated in Figure 1B, inter-sweep-block-intervals and inter-sweep-intervals for CEOAE measurement were 528 ms in duration. Total duration of one sweep was 6.144 s, twenty such sweeps were obtained per participant to acquire 2120 click epochs in total. Clicks were presented in one of the two transducers in the ipsilateral ear (channel-1), and elicitors in the transducer in the contra-channel.

CEOAE - response extraction

All CEOAE processing was done offline. Similar to the SFOAE experiment, the first and last two epochs of every sweep-block were discarded to avoid epochs that occurred during the rise/fall phase of the elicitor. Stimulus reliability was checked across all recorded epochs to remove artifactual epochs. Epochs with ear-canal recorded click stimulus root-mean-square (RMS) amplitudes that were two SD above the mean (within-individual) were rejected. Responses in the time-window from 5-20 ms were extracted, and digitally bandpass filtered from 0.5 to 6 kHz using a fourth order zero delay Butterworth filter to obtain CEOAE and noise metrics. To estimate reliability of data from a given participant, consecutive click epochs across sweeps were collected into two buffers: A and B. A correlation analysis was then performed between the two buffers and served as a measure of reliability. Each CEOAE was calculated as the

mean RMS amplitude of the waveform within the time window. Congruent with the SFOAE experiment, MOC inhibition of CEOAEs obtained in Pascals was expressed as normalized (re: baseline CEOAE level) percent change in CEOAE level (ΔCEn). Noise and SNR were estimated using the formulae:

$$Noise = \sqrt{\frac{abs(bufferA - \bar{X})^2 + abs(bufferB - \bar{X})^2}{2}} \tag{7.1}$$

$$SNR = 10 * log10[(\frac{\bar{X}^2}{Noise^2}) - 1] \tag{7.2}$$

where, $\bar{X}$ is the grand average of responses across all epochs.

DPOAE - stimulus

Primaries, f_1 (from 1231 Hz to 2462 Hz) and f_2 (from 1502 Hz to 3003 Hz) were exponentially ramped at 8 s/octave in one continuous glide[1] to obtain $2f_1$-f_2 DPOAE (f_{dp}) in the frequency range from 960 Hz to 1920 Hz. The frequency difference between primaries were maintained at a constant ratio (f_2/f_1) of 1.22, and levels (L_1/L_2) at 60/50 dB SPL. One sweep-block contained both primaries in two separate channels (1 and 2), and was 8.54 s long. Two consecutive sweep-blocks with an inter-sweep-block-interval and inter-sweep-interval of 676 ms made one complete sweep of 18.432 s. Twenty-one such sweeps were acquired for further offline analysis.

DPOAE - response extraction

First, noisy epochs were rejected to obtain best possible SNR. For this, difference in RMS level across epochs (1.024 s length of data) were compared to reject noisiest epochs. Epochs were rejected until no further decrement in SNR was observed within

[1]Typically, the word 'sweep' is used in the literature to describe a continuous signal presentation where frequency is swept across time. However, to avoid confusion between the previously described 'sweep' which encompasses sweep-blocks, the word glide will be used.

a 5% symmetric level of significance. Following noise rejection, DPOAE response extraction involved unmixing of the two DPOAE components: the distortion component (df_{dp}) and the reflection component (rf_{dp}). Considering the two components are generated by two different mechanisms, the reflection component involves accumulation of phase at the f_{dp} place, while the distortion component does not. This difference in phase characteristics between the two components, and their difference in time of arrival in the ear canal allows for time domain separation of the two components (Kalluri & Shera, 2001; Knight & Kemp, 2001). The mixed response was first considered in the time domain, where the two components can be separated and then individually converted to the frequency domain. Considering DPOAEs obtained in the present study contained exponentially increasing frequencies, a least square fit algorithm (LSFA) described in Long, Talmadge, and Lee (2008) was adapted to obtain amplitude and phase information. The LSFA method uses a model fit to the signal, and input parameters to this model are such that the squared error between the model and original signal are minimized.

MOC elicitor

The MOC activating elicitor was uniform and random broadband noise (BBN) of varying duration (one sweep-block) across OAE types with 20 ms onset/offset ramps to avoid startle responses. Differences in MOC elicitor duration would not be expected to cause any change in MOC activation pattern, considering all sweep-block durations outlast MOC rise time and are sustained for 2 seconds or more (Backus & Guinan, 2006; Berlin, Hood, Hurley, Wen, & Kemp, 1995; Liberman, 1988b). Elicitors were presented at 60 dB SPL, sufficiently below the ART of every participant. Notwithstanding, additional tests (see subsection 7.2.4) were performed to check for middle ear muscle reflex (MEMR) activation.

7.2.4 Test for MEMR

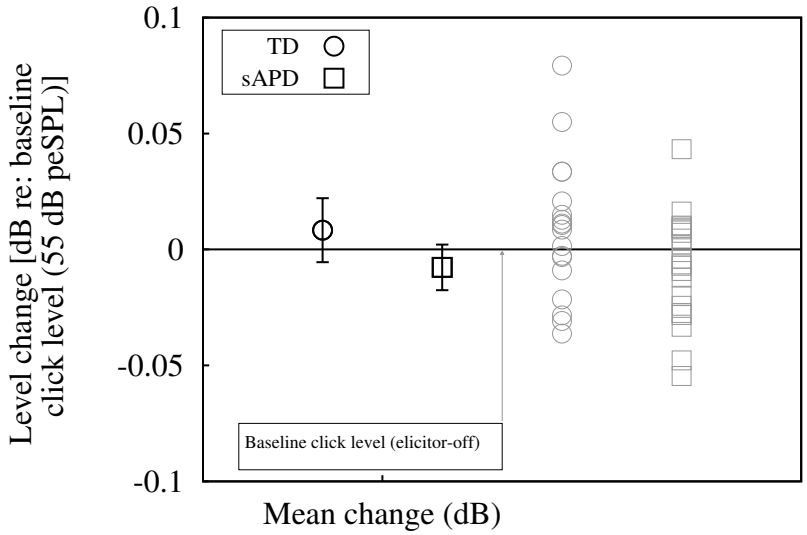

Figure 7-2: Results of MEMR test. Means and their corresponding individual data for the change in stimulus level with reference to baseline no-elicitor condition (dB) is plotted (y-axis). Black straight line in plot A at 0 dB represents normalized baseline stimulus level (in no-elicitor condition. Black symbols are group means with their corresponding 95% confidence intervals represented by error bars. Grey symbols are individual means of RMS amplitude near the stimulus trough. Circles represent TD and boxes represent sAPD.

In addition to recruiting participants only with high enough ARTs (>70 dB HL), click levels were evaluated offline for deviations in level during elicitor presentations (re: no-elicitor condition). This test is based on the hypothesis that a significant MEMR would consistently increase probe-tip stimulus levels. This is because, MEMR activation will stiffen the ossicular chain and retract the tympanic membrane, resulting in increased reflection of stimulus energy back to the ear-canal. A cut-off value of 1.4% (0.12 dB) increase in stimulus level during elicitor-on condition compared to no-elicitor condition has been suggested as an indication of MEMR activation (Abdala, Dhar, Ahmadi, & Luo, 2014; Abdala, Mishra, & Garinis, 2013).

To test for such changes in level, RMS levels of the ear-canal recorded stimulus in a time-window near the first trough of the click waveform (125 μs duration) for elicitor-on/off conditions for every participant were obtained. As seen in Figure 7-2A, changes in the presence of MOC elicitors were on average -0.0003 dB $\pm$0.008 (re: baseline no-elicitor). The largest change in both directions (increase and decrease in amplitude) was $<\pm$0.08 dB. Observed stimulus level deviations occur in both directions, i.e., increase and decrease in level. A level reduction would not be expected if MEMR were to act on the stimulus (Abdala et al., 2013). The observed changes are small compared to level changes that would be expected if the MEMR was activated (Abdala et al., 2014, 2013). These changes probably arise due to random fluctuations in background noise. Note that five children (1 from TD, and 4 from sAPD group) did not undergo this secondary MEMR test due to time constraints. Therefore, in these children, their ART thresholds were used for the evaluation of MEMR activation.

7.2.5 Data inclusion criteria

For data to be considered for statistical analyses the following criteria were applied for all OAE types: (1) <10% epoch rejection, (2) minimum SNR of 9 dB, and (3) no MEMR activation. In addition, for CEOAEs, a correlation coefficient of 0.85 or higher between the two response buffers was also required.

In children who chose to take part in the experiment in two sessions, those with poor SFOAE were not recalled for other OAE measurements, this led to rejection of 14 participants from the sAPD group and two from TD group. A further three from the sAPD group (one due to ART <70 dB HL) and one from the TD group were rejected from the SFOAE experiment based on the data inclusion criteria above. Final sample size for all OAE types are detailed in Table 7-1;

Group	OAE type				
	SFOAE	**CEOAE**	**DPOAE$_m$**	**DPOAE$_d$**	**DPOAE$_r$**
sAPD	30	21	22	22	21
TD	22	18	18	18	16

Table 7-1: n size in all OAE experiments across the two groups. Subscript in DPOAE columns represent their respective generation mechanism; m = composite (distortion + reflection) DPOAE, d = distortion component DPOAE, and r = reflection component DPOAE.

7.3 Results

OAE frequency spectra for all three OAE types are plotted in Figure 7-3 for both TD and sAPD groups. Qualitatively, both groups show reduction in OAE level in the elicitor-on condition, suggestive of MOC mediated change in OAE level. While it is common to display both SFOAEs and DPOAEs in the frequency domain, CEOAEs are often plotted in the time domain. To allow visual comparison of all OAEs, Panel B shows the Fourier transformed frequency domain representation of CEOAEs obtained in the 5-20 ms time-window. As CEOAE level decreased rapidly beyond 2 kHz, only the frequency range 0.5-2 kHz is shown in Panel B of Figure 7-3. However, the entire 0.5-6 kHz range was used for statistical analyses. Considering 41.67 Hz rate was used, correction factors derived in Chapter 3 were applied for MOC inhibition of CEOAEs to account for possible ipsilateral MOC activation:

$$y = 0.108x - 2.7 \ (\%\Delta\text{CEOAE}) \tag{7.3}$$

Where, x here is 41.67, and resultant y is the correction factor to be subtracted from overall MOC inhibition of CEOAEs.

Both groups showed significant ($p<0.001$) MOC-mediated reduction in OAE level

in single sample t-tests, results of which are tabulated in Table 2. All results were interpreted with alpha correction using false discovery rate (FDR: Benjamini & Hochberg, 1995) for performing multiple comparisons.

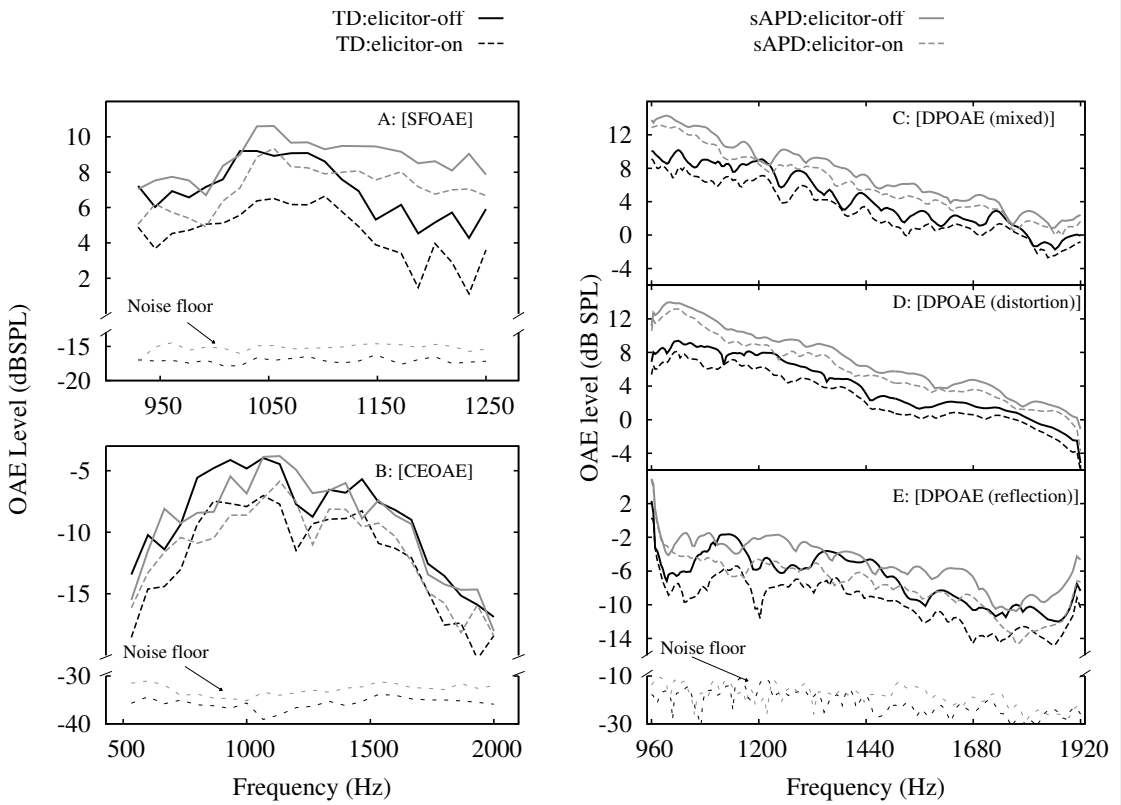

Figure 7-3: Amplitudes of all OAE types (in dB SPL) are plotted in this figure as a function of frequency. SFOAE in plot A, CEOAE in plot B, composite DPOAE in plot C, distortion component of DPOAE in plot D, and reflection component of DPOAE in plot E. In all plots, black lines represent TD data, and grey lines represent sAPD data. Continuous lines represent OAEs in elicitor-off condition and dashed lines represent OAEs in elicitor-on condition. Noise floor for all OAEs are plotted as a function of frequency. Note that mean noise levels of composite DPOAE are plotted in panel E because OAE levels were closest to the noise in this panel. Also note that the y axis of plots A, B and E are not continuous.

Group	Mean MOC inhibition of OAEs (within group)				
	ΔSFn (%)	**ΔCEn** (%)	**mΔDPn** (%)	**dΔDPn** (%)	**rΔDPn** (%)
TD	21.71 (±4.27)	24.42 (±6.97)	14.75 (±4.80)	14.03 (±4.99)	25.34 (±8.00)
t[df], $p<$	10.57[21], 0.001	7.37[18], 0.001	6.47[17], 0.001	5.94[17], 0.001	6.75[15], 0.001
sAPD	16.97 (±2.40)	19.21 (±4.26)	12.60 (±2.44)	12.76 (±2.86)	23.62 (±5.34)
t[df], $p<$	14.50[29], 0.001	9.42[20], 0.001	10.75[21], 0.001	9.27[21], 0.001	9.23[20], 0.001

Table 7-2: Results of single sample t-test. Means and 95% confidence intervals (values in brackets) of normalized MOC inhibition across OAE types are provided in the first row of respective groups. Second rows of each group contain t values, degrees of freedom, and their respective p values.

Mean MOC inhibition across OAE types and groups are plotted in Figure 7-4, and tabulated in Table 7-2. As evident in the figure, and the table, MOC inhibition of OAEs is numerically slightly lower in the sAPD group in comparison to the TD group.

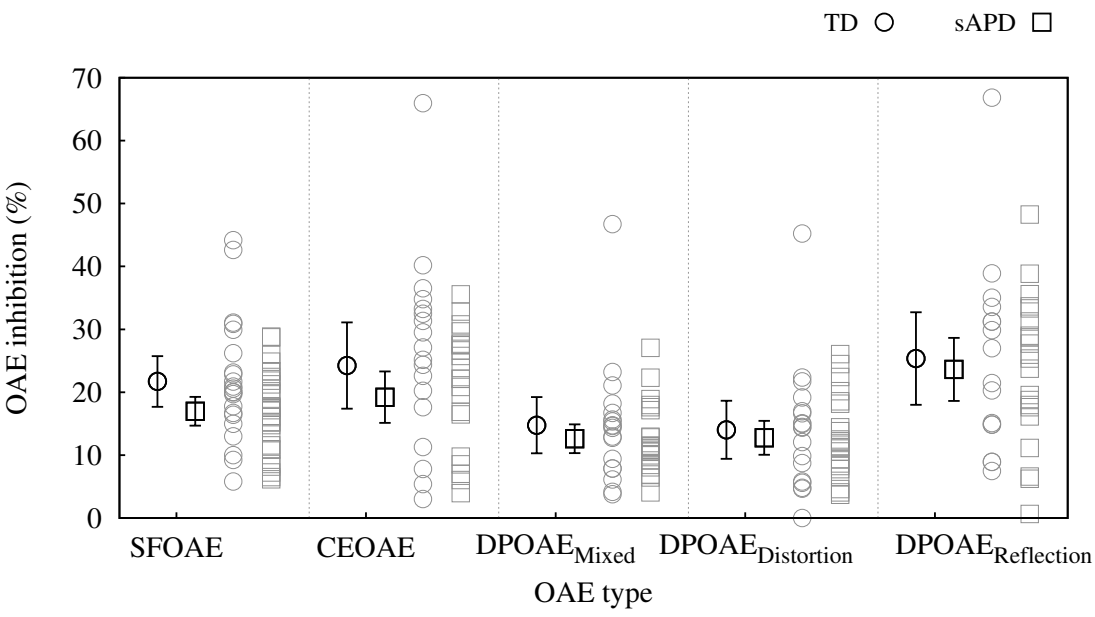

Figure 7-4: Means (black symbols) and individual (grey symbols) data showing magnitude of MOC inhibition of OAEs (normalized change in level re: baseline elicitor-off condition) has been plotted for all OAE types. Circles represent TD group and squares represent sAPD group. Error bars represent 95% confidence interval around the mean.

Individual data in grey shows considerable overlap between the two groups. To investigate group differences in MOC inhibition of OAEs, normalized OAE metrics for all OAE types (ΔSFn, ΔCEn, mΔDPn, gΔDPn, and rΔDPn) were subjected to statistical tests. Analyses were complicated by rejection of participants across OAE types. For instance, participant 'c193' had good DPOAE and SFOAE, but poor CEOAE; on the other hand, participant 'c196' had good SFOAE and CEOAE, but poor DPOAE. If a repeated measures analysis were performed, this type of participant rejection would have led to an n size of only 12. This would significantly reduce the power of the study, undoing the advantage of performing repeated measures ANOVA. To avoid this, groups means were compared using independent sample t-tests for each OAE type separately with corrections for performing multiple comparisons.

	Across group comparison (TD vs. sAPD) for all OAE types				
	ΔSFn (%)	**ΔCEn** (%)	**mΔDPn** (%)	**dΔDPn** (%)	**rΔDPn** (%)
MD	4.74 (±4.47)	5.20 (±7.71)	2.15 (±4.92)	1.26 (±5.30)	1.72 (±8.92)
t[df], p=	2.13[50], 0.038	1.67[38], 0.180	0.88[38], 0.381	0.63[38], 0.633	0.39[35], 0.698

Table 7-3: Results of across group comparison of MOC inhibition of OAEs. Values displayed in the first row are mean differences across groups for each OAE type and their corresponding $CI_{95\%}$ (in brackets) of normalized MOC inhibition. Second row contains t values, degrees of freedom, and their respective p values.

As evidenced in Table 7-3, a group difference in MOC inhibition reached significance only for SFOAEs (p=0.038), however, due to alpha corrections this significance was lost. Current results suggest that although numerically smaller in all OAE types, MOC inhibition is not significantly smaller in the sAPD group.

7.4 Discussion

7.4.1 General discussion

The present study was conducted to reconcile the results of previous studies that show opposing findings on MOC strength in children with APD. Three different OAE types were used for this purpose, CEOAE, DPOAE and SFOAE. Consistent with the inhibitory effect of MOC on OHC activity, both groups (TD and sAPD) showed significant reduction in all OAE types. However, despite numerically smaller MOC inhibition in all OAE types in the sAPD group, none of the OAEs show significant group differences.

There are several potential factors that should be considered. First, there was large variability within each group, leading to considerable overlap in MOC inhibition of OAEs between groups. This is observable in the individual data plotted in Figure 7-4.

Secondly, power calculation based on means and standard deviations obtained from studies that show significant group difference (APD vs. TD) in MOC inhibition of OAEs show that the current study possesses adequate power and sample size. Therefore, sample size is not one of the reasons for non-significant group differences. On the other hand, it should be noted that the sAPD group indeed showed significantly lower inhibition when measured using SFOAEs, but the significance was lost due to alpha corrections for multiple comparisons. Previous studies have either not reported, or not applied alpha corrections (e.g., Sanches & Carvallo, 2006). Therefore, if only SFOAE were used to compare these two groups, one would conclude that children in the sAPD group do indeed have significantly compromised MOC inhibition of OAEs. While the trend does appear that way, the results are variable, within the current study, and across studies.

Another reason for non-significant differences between groups could have stemmed due to inclusion of non-APD children. Unlike previous studies that show significant differences between groups, the current study included children who were deemed as non-APD. This was done based on the findings of Allen and Allan (2014), who showed that children who were deemed non-APD did indeed have listening difficulties, and showed abnormalities in physiological tests such as ABR and acoustic reflex. Separate comparisons of MOC inhibition between children diagnosed as APD and TD children again showed no significant group differences (in ΔSFn for e.g., $t[40]$ = -1.93, p = 0.06). Therefore, addition of non-APD children in the sample probably did not lead to the non-significant group differences between sAPD and TD groups.

The results of all OAE types show non-significant group differences, given the heterogeneity in auditory problems in APD (Moore et al., 2010), it is not surprising that weak MOC is not prevalent in children suspected with APD. Identifying children with weak MOC specifically and profiling their auditory characteristics may shed light on the role of the MOC in such children, rather than attempting to identify such children in an APD group. The question then is, what is considered a weak MOC? Given the variability even in individuals with normal listening, as seen in the present study and various previous other studies (e.g: Backus & Guinan, 2007; Butler et al., 2011), a cut-off limit for strong vs. weak MOC inhibition of OAEs may be difficult to establish. Nevertheless, Muchnik et al. (2004) used cut-off values of 0.6 and 1 dB CEOAE inhibition proposed by Prasher, Ryan, and Luxon (1994) to classify weak vs. strong MOC. Based on these cut-off values, they found that a significantly larger number of children in their APD group fell short of the cut-off, compared to their control group. A more recent look at the distribution of MOC strength in normal listening individuals was carried out by Backus and Guinan (2007). They also found MOC strength to vary considerably across their sample, however it followed a normal distribution

with a mean strength of 35±12% (reduction in OAE level due to MOC activation). Considering Backus and Guinan (2007) used an SFOAE assay which included phase information (vector) in their MOC strength calculation, a direct comparison is not possible with the current study (TD group: 21±10%). The current study obtained only the scalar part of the SFOAE level, no phase information was included in calculation of SFOAE magnitude. For example, if a cut-off of mean (TD group) minus 1 SD of ΔSFn was considered as weak MOC, 8/30 (26%) children in the sAPD group fall below the cut-off, while 2/21 (9%) children in the TD group fall below the cut-off. Therefore, despite the lack of significant group differences, the current study does not completely dismiss the idea that MOC strength may be weaker in some children with listening difficulties. Based on current results, it appears that children in the sAPD group are more likely to have a weak MOC system, despite the considerable overlap between the two groups. However, evaluating MOC strength may not be a viable clinical test for diagnosing APD, at least as APD is currently defined.

As mentioned earlier, there is considerable difference in diagnosis of APD across clinics. For instance, Muchnik et al. (2004) included educational and/or behavioral symptoms as a diagnostic marker in addition to an APD test battery. Sanches and Carvallo (2006) on the other hand used only SSW test to diagnose APD. While there are specific tests that audiology professional bodies recommend for use as APD tests, the list is vast, and is subject to clinician selection. There are also no gold standards in APD diagnosis. Furthermore, considering most APD tests in typical test batteries tap higher auditory function, separating children based on these tests may not be a suitable marker to test for reduced MOC function, a brainstem mechanism. This is because, although MOC is influenced by corticofugal connections, MOC assays typically use a noise elicitor to activate and investigate the MOC reflex, where the cortical influence is minimal (de Boer & Thornton, 2007). Therefore, if one is

interested in identifying anatomical underpinnings of APD, recruiting children based on the 'umbrella-term' APD may not suffice. Further sub-classes of APD could be created and their specific physiological characteristics could be studied. An example is the one created based on difficulties in spatial processing (Cameron, Dillon, & Newall, 2006). Dillon (2012) suggested using a hierarchical pathway in diagnosis and treatment of APD. In order to probe for biological markers of APD, including MOC function, such a diagnostic pathway might become useful. To identify children with specific difficulties, for example, if they failed gap detection tests, further temporal processing tests can be performed to evaluate the problem in question. If temporal problems are consistent across behavioral tests with no other auditory problems, an objective test to probe for a biological marker of the observed temporal difficulties can be initiated using neural response fidelity tests such as speech ABR (Banai & Kraus, 2007). This method of testing children, at least for research purpose, may aid in identification of underlying physiological anomalies.

7.5 Conclusion

The present study aimed to elucidate if MOC inhibition of OAEs is affected in children with listening difficulties. Also, with the use of three different OAEs, reconciliation of results of previous studies that show opposing views was attempted to obtain a coherent view on this topic. Results indicate that although the sAPD group shows numerically smaller MOC inhibition of OAEs in comparison to the TD group, they were not statistically significant at a group level. However, these results do not dismiss the notion that *some* children with listening difficulties may have reduced MOC function. An alternative means to grouping children based on their auditory difficulties rather than a generic diagnosis such as APD may facilitate identification of specific biological markers.

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Chapter 8

Spatial Hearing Abilities in Children with Suspected Auditory Processing Disorder

8.1 Introduction

The acoustic environment of a typical classroom has been studied by several investigators (eg: Crandell & Smaldino, 2000; Crukley, Scollie, & Parsa, 2011; Knecht, Nelson, Whitelaw, & Feth, 2002; Nelson & Soli, 2000). Unequivocally, all these studies suggest that the noise levels in typical classrooms are higher than recommended limits, and the signal-to-noise ratios (SNRs) can be as low as -7 dB (Crandell & Smaldino, 2000). At such low SNRs, children are faced with the daunting task of separating noise from speech in order to learn and carry out effective communication. Howard, Munro, and Plack (2010) showed that even children with good listening abilities expend considerable listening effort in typical classroom SNRs, and as a result, make more errors while performing dual tasks. Despite such unfavorable acoustics, most children are able to perform well in school, but about 2-3% of children are unable to follow conversations in noise (Chermak & Musiek, 1997). These children are typically referred to audiology clinics where they are tested for the presence of auditory processing disorder (APD). Although there is no clear consensus on what does or does not constitute APD and its diagnosis, children with listening difficul-

ties typically undergo a test battery assessment (American Academy of Audiology [AAA], 2010; American Speech-Language-Hearing Association [ASHA], 2005). The test battery approach has recently been criticized for its inefficiency (Dillon, 2012). This is primarily because, a simple pass/fail in the behavioral test battery does not necessarily guarantee correct identification of children with genuine listening difficulties (Allen & Allan, 2014; Dillon, 2012). Dillon (2012) pointed out that assessing children with such a vast selection of tests increases the probability of failing in a test, and may also cause fatigue due to performing large numbers of tests. Dillon (2012) suggested a hierarchical approach to APD diagnosis for identifying the underlying problem, rather than for application of the diagnosis itself.

As an example of a specific underlying problem, Cameron, Dillon, and Newall (2006) identified a sub-category of children with listening problems who did not benefit from spatial separation of speech and noise using a novel test called Listening in Spatialized Noise (LiSN: Cameron & Dillon, 2008). The LiSN tests for perceptual parsing of sound streams based on both spatial segregation (spatial separation of masker and target) and vocal segregation (difference in speaker quality between masker and target) (Cameron & Dillon, 2008). Spatial separation of speech and noise is useful because it offers an improvement in speech perception compared to co-located sounds; this is called 'spatial release from masking' (SRM: Freyman, Helfer, McCall, & Clifton, 1999; Hawley, Litovsky, & Colburn, 1999). SRM has been shown to occur in both adults and children even as young as 3 years of age (Garadat & Litovsky, 2007). Binaural hearing plays a key role in SRM (Kidd, Mason, Rohtla, & Deliwala, 1998), which in turn aids auditory stream segregation (Bregman, 1993).

Spatial separation of speech and noise is achieved in the auditory system through at least four processes: (1) binaural unmasking (discussed below) that provides re-

lease from masking for both energetic (Bronkhorst, 2000) and informational[1] (Kidd et al., 1998) masking, (2) the head-shadow effect occurs because at least one ear receives larger SNR (Zurek, 1993), (3) binaural summation (when signals arriving from the front achieve greater representation in the system due to their presence in both ears), and (4) envelope cues from maskers. The head-shadow effect has been thought to account for a large proportion of masking release from energetic masking, and binaural cues are thought to be more important in informational masking release. Binaural unmasking occurs when the auditory system exploits interaural time difference (ITD) cues to compare and selectively improve the binaural signal to noise ratio (Culling & Akeroyd, 2010). Considering speech and noise typically overlap in both temporal and spectral domains (Arbogast, Mason, & Kidd, 2002; Saberi, Dostal, Sadralodabai, Bull, & Perrott, 1991), spatial unmasking may provide the best SNR compared to other biological noise reduction mechanisms because noise and speech are separated at the level of the source.

The timing cues (ITD) that promote SRM also, in part, govern sound localization. However, ITDs are important only for low frequencies, and its sound level counterpart (interaural level difference: ILD) plays a crucial role at high frequencies. Both ITD and ILD play a critical role in azimuthal or horizontal plane localization, while spectral cues induced by pinna, head and torso filtering of high frequency sound facilitate median plane, i.e., front/back (F/B) and up/down (U/D) localization (Culling & Akeroyd, 2010; Grothe, Pecka, & McAlpine, 2010; Middlebrooks & Green, 1991). Localization aids in the formation of auditory streams that aids speech perception, especially when masked by informational maskers (Kidd, Arbogast, Mason, & Gallun, 2005). It is thus clear that localization and SRM are essential for achieving better

[1]Informational masking occurs when a signal threshold is elevated for reasons unexplained by peripheral overlap of signal and masker. It is thought to arise due to uncertainty related to the masker (Lutfi, 1990).

SNR in adverse listening conditions.

Despite being indicated as one of the processes that can be affected in children with APD, there is a startling lack of evidence on localization abilities in this population (AAA, 2010; ASHA, 2005). Localization and localization-in-noise has received little or no attention in the APD domain. Indeed Domitz and Schow (2000), using factor analysis, showed that localization, lateralization and other binaural tests are less commonly performed, despite recommendations from professional bodies. With the exception of two unpublished theses (Wakeham, 2008; Zakaria, 2007), there are no other studies that have investigated localization in children with APD. Wakeham (2008) studied the localization ability of 7-12 year old children with APD in free field with a speech-babble masker. He found that children with APD performed poorer than their age matched controls, but cautioned the interpretation of his results due to considerable overlap in localization ability between the two groups. He concluded that any deviation in the localization abilities of children with APD are sub-clinical, and may not lead to difficulties in day-to-day activities. Zakaria (2007) on the other hand found that children with APD performed on par with controls in azimuthal localization but performed poorer in median plane localization. Presently it is unclear as to what aspect and to what extent localization is affected in children with APD. It is also unclear what localization metrics were used by the two previous studies to quantify localization errors. It is also unknown how different noises affect localization in children with APD, and what signal-to-noise ratio is required for accurate localization. In order to address these questions, the present study sought to understand if children suspected with APD have problems in localizing speech in noise by comparing them to localization abilities of typically developing (TD) children. Localization ability of a speech token ('baseball') was investigated in three SNR conditions (-12, -6, and 0 dB) for two different maskers: broadband noise (BBN) and speech babble

(SB). The Hearing In Noise Test (HINT: Nilsson, Soli, & Sullivan, 1994) was used to measure speech perception ability in noise, and obtain SRM. Further, to obtain ITD sensitivity, a just noticeable difference task was also performed under headphones.

8.2 Method

8.2.1 Participants

Forty-seven children in the age range 7-17 years, twenty-one TD children (TD group; mean age = 11.4 years, standard deviation (SD) = 2.4 years, 13 females) and twenty-six children referred to our in-house Audiology clinic with listening problems took part in the study (sAPD group; mean age = 9.9 years, SD = 2.8 years, 8 females). All children had normal middle ear function as determined by clinical tympanometry (GSI-TympStar, Grason-Stadler Inc., MN) and hearing thresholds of 20 dB HL or better at octave intervals between 0.25 and 8 kHz measured using a clinical audiometer (GSI-61, Grason-Stadler Inc., MN). Children also underwent a screening DPOAE measurement (Integrity v-500, Vivosonic Inc., ON) to confirm the presence of OAEs, as an indication of normal peripheral auditory function.

Children in the sAPD group underwent a test battery similar to that used by Allen and Allan (2014) that included three standard clinical tests: the Staggered Spondaic Word Test (SSW; Katz, 1998), Words in Ipsilateral Competition (WIC; Ivey, 1969) and Pitch Pattern Sequence test (PPS; Pinheiro, 1977), and two psychoacoustic tests that use adaptive procedures developed in-house for use with children: Gap Detection (GD), and Difference Limen for Frequency (DLF). Tests were administered in accordance with their respective manuals and were interpreted according to published age-specific normative data. Of the 26 children in the sAPD group, 16 were diagnosed as having APD based on ASHA (2005) guidelines, i.e., scored 2 standard

deviation (SD) below the normative expectation in at least two tests. Eight children failed in one test, and two children passed all tests. Of the 10 children who passed all or all-but-one behavioral measures, all had atypical ABR in the form of prolonged peak latencies; prolonged inter-peak latencies; or abnormal wave I-V amplitude ratio. Abnormalities in ABR have been recently reported in children suspected with APD. A recent study (Allen & Allan, 2014) showed that behavioral tests alone may not be adequate in diagnosis of APD, which supports recommendations by professional bodies (e.g., AAA, 2010). Allen and Allan (2014) found several children who passed these behavioral tests had abnormal neural encoding of sound measured using ABR and/or absent/elevated acoustic reflex thresholds. Therefore, children who passed the behavioral test battery but who had abnormal ABR were also included in the study group (sAPD) along with children diagnosed as APD.

Study methods were approved by the Health Sciences Research Ethics Board of Western University, Canada. The nature of the study was explained prior to obtaining written informed assent from every participant, and informed consent from the participants' parent/caregiver. Participants were compensated for their time.

8.2.2 Localization experiment

The experimental set-up of loudspeakers for the localization experiment is illustrated in Figure 8-1. The experiment was conducted in a hemi-anechoic chamber (Eckel Industries, ON, Canada). Targets were presented from 8 loudspeakers placed 45° apart in the presence of a diffuse noise field. Participants stood at the center of the loudspeaker array facing the 0° azimuthal loudspeaker. Maskers were BBN (uniform and random) and SB. SB was created by concatenating two sentences from the HINT sentence corpus (Nilsson et al., 1994). Four different sentence pairs formed a four-channel masker that was presented simultaneously at a sampling rate of 44.1 kHz

in free-field using loudspeakers positioned at azimuths of 45°, 135°, 225°, and 315° (loudspeakers just beneath the ones marked with asterisks in Figure 8-1). This set-up produced a diffuse noise field that avoided the effect of masker location on the obtained localization responses (Lorenzi, Gatehouse, & Lever, 1999). Similarly, BBN was presented from the same four loudspeakers during the BBN noise condition.

Stimulus

The target stimulus was a 600 ms long speech token ('baseball') spoken by a native Canadian speaker from south-western Ontario (Grieco-Calub & Litovsky, 2012). The speech token was recorded in a sound attenuated audiometric booth using a studio-grade AKG condenser microphone (Type C 4000B) at 44.1 kHz, and later up-sampled to 48.828 kHz using Praat (Boersma, 2002) to match the sampling rate of the localization rig. This speech target was chosen because of its relevance to the real world and the fact that F/B confusions occur more often with speech, compared to broadband or click targets (Gilkey & Anderson, 1995). The use of two different loudspeaker arrays to present noise and speech targets avoided any electrical mixing of signals. Maskers were looped continuously for a single block duration. Each block, obtained by roving the target level in random order, contained 40 stimulus presentations (trials) at three different SNRs (-12, -6, and 0 dB). Three such blocks were completed for each participant for each masker condition to obtain 5 responses per SNR condition for every azimuth. In total, 120 trials (8 loudspeakers x 3 SNRs x 5 repetitions) were shuffled and divided into three blocks. One block of trials was performed in quiet to obtain baseline localization ability. The target was presented from any one of the 8 loudspeakers placed 45° apart, starting at 0° in a 16-channel loudspeaker array (see Figure 8-1). Using a reference microphone placed at center of the array, the root-mean-square (RMS) amplitudes of the maskers were matched, and were presented constantly with a combined level of 66 dB SPL throughout the

experiment. Each target stimulus presentation was initiated by a button press by the investigator standing outside the loudspeaker array, with the participant facing the 0° azimuth loudspeaker. All stimuli were calibrated using a Type-2250 sound level meter (Brüel and Kjær, Denmark) with the microphone placed at ear level in the center of the loudspeaker array. A potential caveat in the use of a single target is that the task may be easier than real life localization of speech. On the other hand, especially in children, using a single target reduces uncertainty and may avoid the use of high level cognition-based processes for the task.

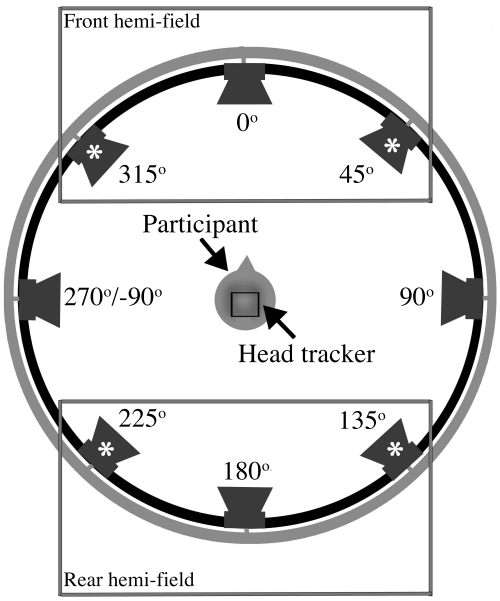

Figure 8-1: Schematic representation of the loudspeaker array for the localization experiment. Maskers were presented simultaneously through four loudspeakers placed just beneath loudspeakers marked with asterisks. Participants stood in the center of the circular array, the radius of which was 1.5 m. The electromagnetic head tracker transmitter was positioned above and behind the participant's head, and the tracker sensor was mounted on a custom made plastic helmet worn by the participant.

Instrumentation

Maskers were played through a multi-channel sound interface (Audiofire12; Echo Digital Audio Corp., CA) to four separate channels of a networked signal processor (SoundWeb9008; BSS Audio, Hertfordshire, UK) which was amplified by CX18 amplifiers (QSC Audio, CA) before being fed to four Tannoy i5AW loudspeakers placed just below the loudspeakers marked with asterisks in Figure 8-1. The speech target was played through a real-time signal processor (RX6; Tucker-Davis Technologies, FL) for digital-to-analog conversion before following the same (equipment) route as the maskers, and finally to one of eight loudspeakers. Participants stood in the middle of the loudspeaker array on an adjustable stand, such that the target loudspeakers were at ear level. They were fit with a custom-made adjustable plastic helmet with a focused red LED light beam that guided them in pointing to the response azimuth. Participants were instructed to turn their head and point the red LED light to the loudspeaker from which they thought the word 'baseball' had emanated. The helmet also carried the sensor for an electromagnetic head tracker device (Frastrak, Polhemus, VT) that recorded the head position with reference to 0° azimuth. Head position was recorded upon a button press by the investigator using a custom-made response box. The head-tracker was connected through a serial data line to a head tracker interface (HTI3; Tucker-Davis Technologies, FL), which then fed the data to the RX6 real-time signal processor via a fiber optic connection. The button box was directly connected to the RX6, where the button-press and corresponding azimuth information was stored in a personal computer.

Measures to quantify localization ability

Example localization data obtained from a child participant are shown in Figure 8-2. Two measures were obtained to quantify the localization performance of each participant in each listening condition. The first was front/back percent correct (FBpc),

which is the percentage of correct identification of sounds arriving from the front or rear hemifields. To calculate FBpc, only responses to targets with azimuths between -67.5° to 67.5° (front hemifield) and between 112.5° to 247.5° (rear hemifield) were considered, illustrated as boxes in Figure 8-2A. The FBpc measure provides an estimate of F/B percent correct responses within the correct hemi-field, independent of the accuracy of the response. FBpc was used instead of an overall localization error because: (1) lateral angle localization is resilient to noise, and it is the median plane localization that is most affected (Good & Gilkey, 1996), especially for a speech target, (2) A metric based on RMS azimuthal error (e.g., Abouchacra, Emanuel, Blood, & Letowski, 1998; Good & Gilkey, 1996; Van Deun et al., 2009) is not informative about the type of error, i.e., F/B vs. lateral.

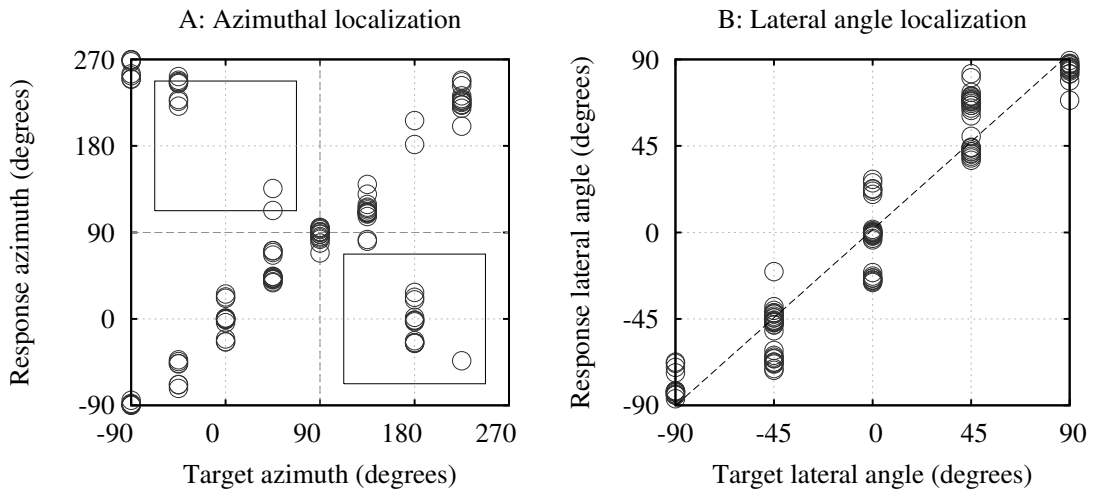

Figure 8-2: Example of localization data from a child participant and analysis methods. The plot on the left [A] shows responses to all tested azimuths on the y-axis and their corresponding target azimuths on the x-axis. Responses on or within the small black boxes are counted as F/B errors. The plot on the right [B] shows only the lateral-angle (L/R) components of the target and response locations, and is essentially a re-formatted version of A, such that if A were folded along the dashed lines running through its center, it would place rear and front hemi-fields in one quadrant. The RMS distance of individual responses from this line provides an estimate of Lscat.

The second measure was lateral scatter (Lscat), which is the RMS angle difference between every response and a linear regression model fit to the data. To calculate this measure, response and target azimuths from both hemi-fields (Figure 8-2A) were reduced to their lateral-angle (left/right) components lying between $-90°$ and $90°$, i.e., one hemi-field (Figure 8-2B). This is akin to folding Figure 8-2A horizontally at $90°$ on the y-axis and vertically at $90°$ on the x-axis along the dark-grey dashed lines to reflect each target and response azimuth into the frontal hemisphere. The resulting plot places all responses within the first quadrant ($-90°$ to $90°$), as shown in Figure 8-2B. This measure estimates the mean consistency of responses across trials.

8.2.3 Lateralization experiment

A just noticeable difference task was carried out with participants to obtain ITD thresholds. Two noise bursts of 500 ms in duration, and 60 dB SPL in level served as stimuli. Noise-bursts were generated in real-time with variable ITD per presentation from a computer using a custom-built Matlab program. Signals were then passed through an Audiofire (Echo Digital Audio Corp., CA, USA) for digital-to-analog conversion before delivery to Sennheiser HD-Pro headphones.

Upon hearing the stimuli, children were instructed to click either the 'right' or 'left' button on a computer screen (with a mouse) to indicate whether the bursts moved from left to right or right to left, respectively. The ITD of the first noise-burst was also randomly roved. Children were able to indirectly indicate if they perceived an apparent difference in ITD between the two noise bursts. The initial inter-burst ITD difference was 1600 μs (one ear leading by 800 μs in the first interval, and the other leading by 800μs in the second). The leading ear in the first burst was chosen randomly from trial to trial and the second burst in the opposite ear led by the the same amount. Threshold tracking was based on the 2-down, 1-up rule. Initial ITD was reduced progressively on a geometrical scale by the factor current-step-size/$\sqrt{2}$

for every correct response. For every incorrect response, the ITD was increased by the factor $\sqrt{2}X$current-step-size. The experiment continued until ten reversals were obtained. The average of inter-burst ITD difference from the final six reversals was considered as the ITD threshold. Visual reinforcement was provided for both correct and incorrect responses. The on-screen button turned green for the correct response, and turned red for an incorrect response. No training was provided, and only one run per participant was conducted in consideration of the time taken for participants to undergo all experiments. The experiment was conducted in the same hemi-anechoic chamber used for the localization experiment.

8.2.4 HINT: Spatial Release from Masking

The commercially available HINT test was automated using custom programs written in C# (Ibrahim, Parsa, Macpherson, & Cheesman, 2012). The HINT was performed in a sound attenuated audiometric booth, in a sound field setting. Speech sentences and noise were passed through an Audiofire for the digital-to-analog conversion from a computer running the HINT software. The analog signal was then fed to four separate PA5 attenuators (one each for speech, and noise at three azimuths), and then amplified by a CX168 amplifier. Signals were then delivered to four Nucleus loudspeakers (AnthonyGallo Acoustics, CA, USA), with two loudspeakers placed at 0° (one for speech and one for noise), and one each at 90°, and 270°. Speech was always presented from the loudspeaker at 0°, but noise was presented for each condition from the three different azimuths at 65 dBA SPL. Two trials of twenty sentences in each noise condition were completed with every participant. Speech level was adapted by ±2 dB for every incorrect or correct response, respectively. A reception threshold for sentences (RTS) score was calculated based on standard HINT procedures (Nilsson et al., 1994), at a 50%-correct performance level. Briefly, the final five response levels and an additional 21^{st}, predicted response (-2 if the 20^{th} response is correct and vice

versa) were averaged to obtain a final RTS score. Noise level (65 dBA SPL) was subtracted from the RTS score to obtain an SNR score. The SNR score indicates the SNR at which children were able to perform at 50%-correct level. Average SNR of two trials was considered for statistical analyses. Therefore, there were three SNR scores for the three noise azimuth conditions (0°, 90°, and 270°).

8.3 Results

8.3.1 Localization

Figure 8-3 shows individual localization data for FBpc in the top two rows for TD (8-3A through D) and sAPD (8-3E through H) groups, and Lscat in the bottom two rows for TD (8-3I through L) and sAPD (8-3M through P) groups. Columns in Figure 8-3 represent SNR conditions, and data are plotted as a function of age. Larger FBpc scores, and smaller Lscat scores indicate good localization performance. An effect of SNR can be seen for FBpc and Lscat in both TD and sAPD groups. An increase in SNR causes an improvement in FBpc and reduces Lscat, but no effect of age can be observed. Considering many children obtain 100% FBpc, slope (described below) of improvement in scores as a function of SNR was subjected to regression analyses to investigate any systematic effect of age. Age was the independent variable and both FBpc (BBN and SB maskers) and Lscat (BBN and SB maskers) slopes were dependent variables. This analysis did not show any systematic age effect for both TD (BBN: $\beta = 0.08$, $t[18] = 1.33$, $p = 0.199$; SB: $\beta =$ -0.08, $t[18] =$ -1.56, $p = 0.134$) and sAPD (BBN: $\beta = 0.04$, $t[23] = 0.58$, $p = 0.565$; SB: $\beta =$ -0.01, $t[23] =$ -0.27, $p = 0.788$) groups. The same analysis was done for Lscat scores for TD (BBN: $\beta =$ 0.002, $t[18] = 0.065$, $p = 0.949$; SB: $\beta = 0.02$, $t[18] = 0.608$, $p = 0.55$) and sAPD (BBN: $\beta = 0.02$, $t[23] = 0.45$, $p = 0.654$; SB: $\beta =$ -0.01, $t[23] =$ -0.07, $p = 0.724$) groups. Considering no age trends were found, data for both groups were collapsed

across age for further analyses.

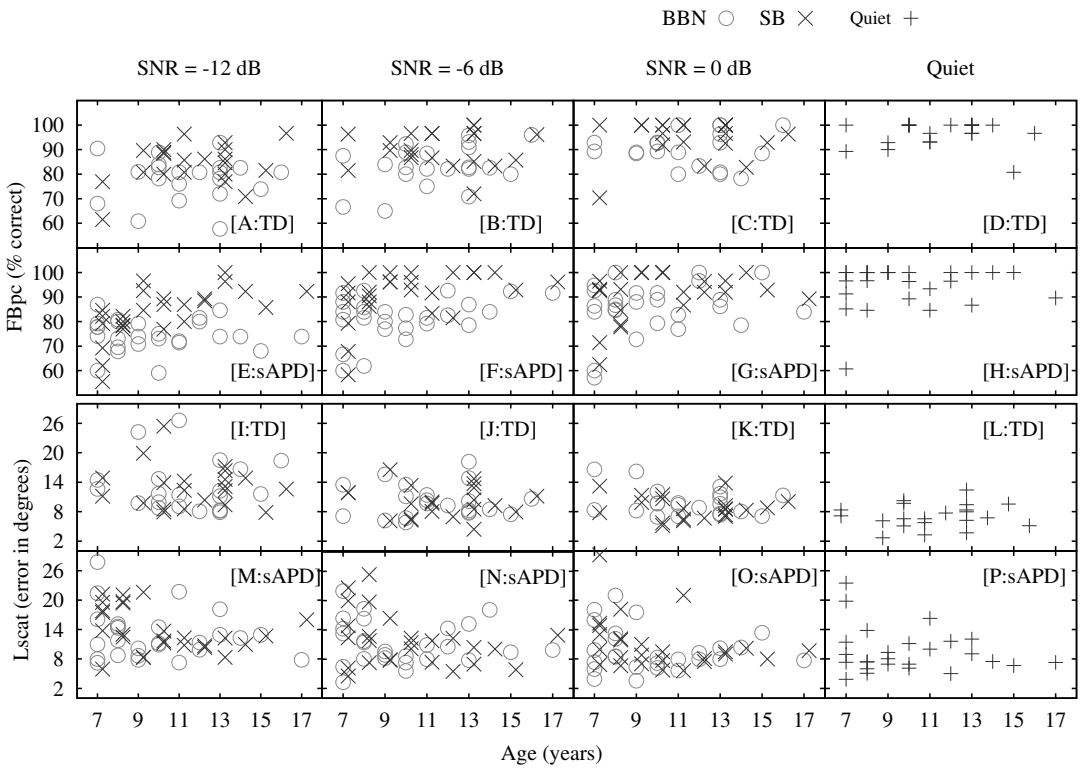

Figure 8-3: Individual scores for both FBpc and Lscat are plotted for both masker conditions and the quiet condition (pluses) as a function of age (years). Circles indicate the BBN, and crosses indicate the SB masker. The top two rows show FBpc data, while the bottom two rows show Lscat data. TD group data for FBpc are shown in the topmost row, and Lscat in the third row. Second and fourth rows show the sAPD group data for FBpc and Lscat, respectively. Columns differentiate SNR conditions. Labels A through P are used in the text to refer to individual panels.

Individual FBpc and Lscat for every participant and corresponding group means as a function of SNR are plotted in Figure 8-4. As evidenced in the Figure 8-4C, gross front-back localization in quiet is equally good in both groups. Average FBpc was 96.47±2.16% (95% confidence interval [$CI_{95\%}$]) in the TD group and 94.28±3.39% in the sAPD group. An independent sample t-test, interpreted with false discovery rate

(FDR: Benjamini & Hochberg, 1995) corrections for multiple comparisons, showed no group differences ($t[45] = 1.01$, $p = 0.320$) for FBpc in quiet. Lscat in quiet in the TD group was 7.08±1.04%, and, as seen in Figure 8-4F it is slightly higher at 9.55±1.76% in the sAPD group. Although this difference was significant ($t[45] =$ -2.23, $p = 0.031$), the significance was lost due to FDR corrections.

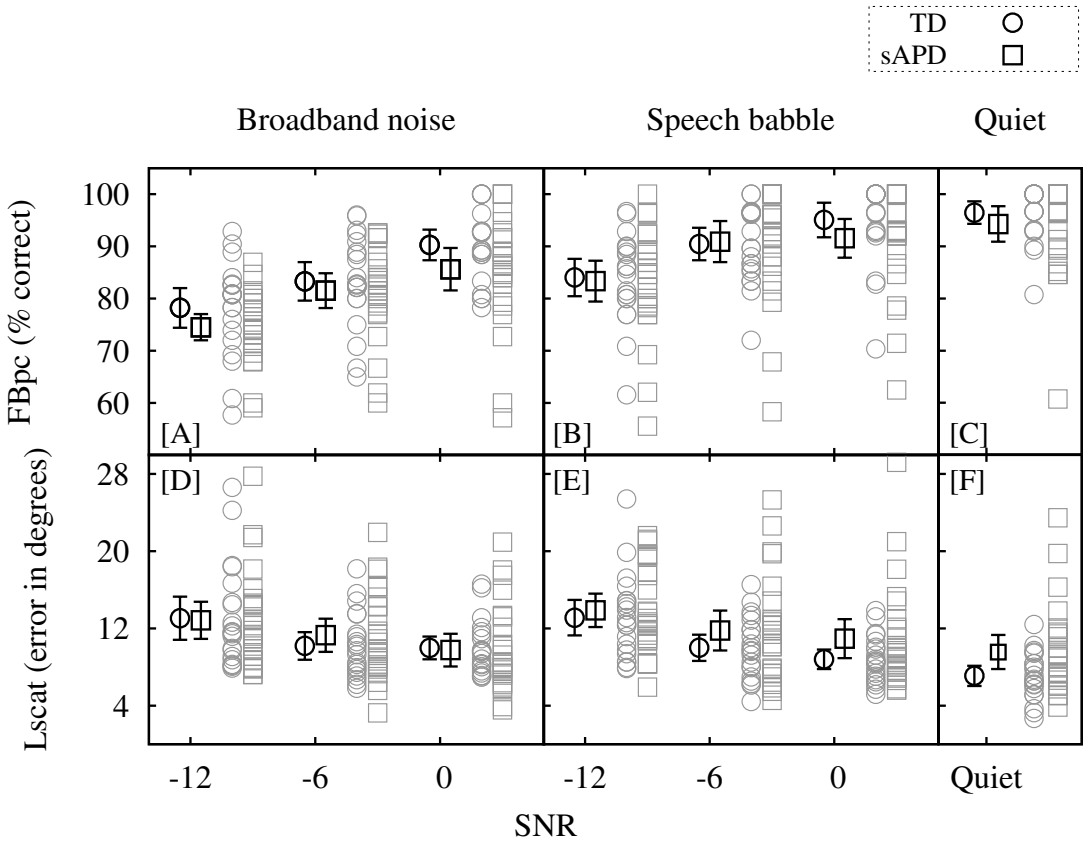

Figure 8-4: Individual scores (grey symbols) and means (black symbols) for both FBpc and Lscat are plotted for both masker conditions and the quiet condition as a function of SNR. Circles indicate the TD group, and squares indicate the sAPD group. The top row shows FBpc data, while the bottom row shows Lscat data. Columns differentiate masker conditions. Labels A through F are used in the text to refer to individual figures.

Collectively, results of FBpc and Lscat in quiet suggest that baseline (in-quiet) localization levels for the two groups are not different. As evident in Figure 8-4A,

localization performance improves as a function of SNR for both groups. Mean FBpc ranged from 78.21±3.8% at -12 dB SNR to 90.28±2.9% at 0 dB SNR for BBN in the TD group. The slope (rate) of this improvement was 1.01±0.29%/dB. Despite slightly lower FBpc values, a similar improvement was seen in the sAPD group, for whom FBpc ranged from 74.51±2.51% at -12 dB SNR to 85.62±4.07% at 0 dB SNR for BBN. The slope of this improvement in FBpc across SNR in the sAPD group was 0.92±0.33%/dB.

FBpc performance was better in SB as compared to BBN (Figures 8-4A and 8-4B), for both groups, as would be expected based on the low-pass characteristic of SB. However, FBpc improvement in SB as a function of SNR followed the same trend as BBN in both groups (Figure 8-4B). In the TD group, FBpc improved from 84.04±3.6% at -12 dB SNR to 95.07±3.3% at 0 dB SNR. The slope of this improvement was 0.91±0.25%/dB. Similar FBpc values were obtained in the sAPD group, and improved from 83.34±3.92% at -12 dB SNR to 91.56±0.9% at 0 dB SNR, which had a slightly shallower slope of 0.68±0.25%/dB.

Lscat-in-noise appears markedly similar between the two groups, and unlike FBpc, Lscat appears similar for both maskers. In the TD group, Lscat improved, i.e., reduced, from 13.05±2.2° at -12 dB SNR to 9.98±1.2° at 0 dB SNR for BBN and from 13.10±1.8° at -12 dB SNR to 8.79±1° at 0 dB SNR for SB. Similarly in the sAPD group, Lscat for BBN was 12.83±1.92° at -12 dB SNR and 9.75±1.69° at 0 dB SNR. For SB it was 13.87±1.74° at -12 dB SNR and 10.93±2.02° at 0 dB SNR. Respective slopes for Lscat were -0.26±0.16%/dB for BBN, and -0.35±0.13%/dB in SB for the TD group, and -0.26±0.18%/dB in BBN and -0.24±0.16%/dB in SB for the sAPD group.

To ascertain SNR, masker, group effects, and interactions, a split-plot (mixed design) ANOVA (SP-ANOVA) with localization measures (FBpc and Lscat) as dependent variables and masker, SNR, and group (TD vs. sAPD) as independent variables was performed. Results were interpreted with Greenhouse-Geisser corrections if the assumption of sphericity was violated. Post-hoc tests were interpreted with FDR corrections ($\alpha = 0.05$) for performing multiple comparisons. Results indicate a significant main effect of masker for FBpc ($F[1,45] = 39.10$, $p<0.001$, $\eta^2_{Partial} = 0.46$), but not for Lscat ($F[1,45] = 3.70$, $p = 0.348$, $\eta^2_{Partial} = 0.02$). This result suggests that when data were pooled across SNRs and groups, there was a significant difference in FBpc between the two maskers. A post-hoc test across maskers (SNRs and groups collapsed) showed that BBN caused significantly larger (Mean difference [MD] = -6.99%, $CI_{95\%} = \pm$ 2.25%, $t[46] = -6.39$, $p<0.001$) disruption in FBpc compared to SB.

There was also a significant main effect of SNR for both FBpc ($F[2,90] = 89.28$, $p<0.001$, $\eta^2_{Partial} = 0.67$) and Lscat ($F[2,90] = 37.27$, $p<0.001$, $\eta^2_{Partial} = 0.45$). This result suggests that, when data were pooled across maskers and groups, localization performance improved as a function SNR, as expected and evidenced in Figures 8-4A, B, D and E. There was no interaction between masker X SNR for FBpc ($F[2,90] = 1.69$, $p = 0.189$, $\eta^2_{Partial} = 0.04$) or Lscat ($F[2,90] = 0.140$, $p = 0.869$, $\eta^2_{Partial} = 0.004$). There were also no two-way (masker X group or SNR X group) or three-way (masker X SNR x group) group interactions for both FBpc and Lscat. Collectively, the results suggest that children in the sAPD group perform on par with TD children.

8.3.2 Lateralization

Similar to FBpc and Lscat analysis, a regression with age as independent variable and ITD scores as dependent variable did not show any effect of age in both TD [$\beta = 0.08$, $t[18] = -107.31$, $p = 0.272$] and sAPD [$\beta = 0.08$, $t[22] = 95.83$, $p = 0.452$]

groups, therefore data were collapsed across age for further analyses. A histogram of the lateralization data is shown in Figure 8-5A. Due to a software limitation, the smallest ITD threshold value attainable was 60.34 μs. Nine of 21 TD children and 3 of 25 children suspected of APD obtained this value and possibly had lower thresholds. One child did not complete the ITD task due to time restrictions.

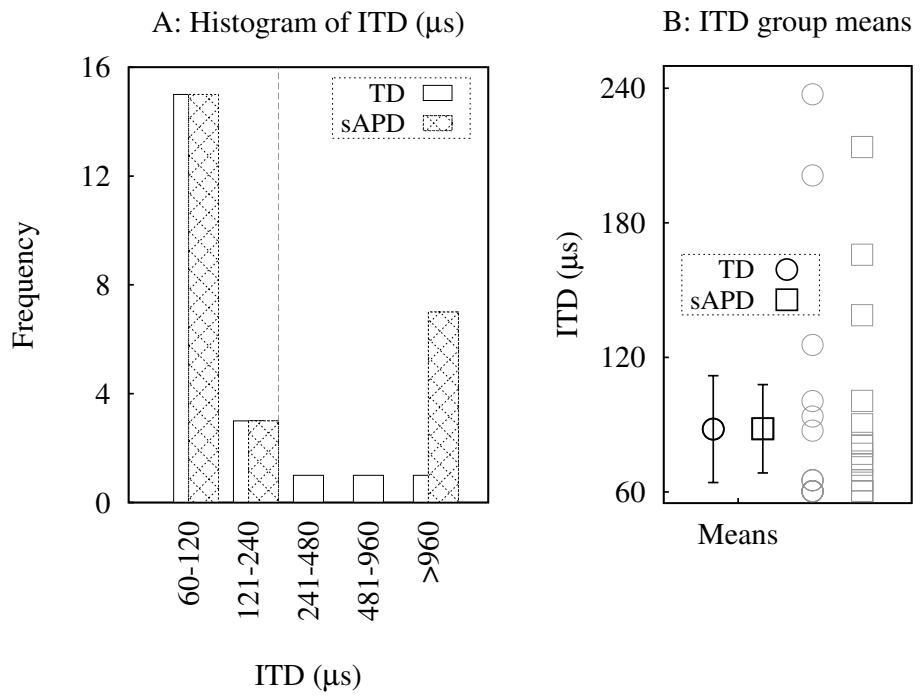

Figure 8-5: A Histogram of ITD thresholds for both groups [A] is presented. Frequency of occurrence of ITD (μs) thresholds are plotted across intervals of ITD threshold bins. The grey dashed vertical line indicates a cut-off point; ITD thresholds beyond this cut-off were considered outliers. Group means (black symbols) and individual (grey symbols) ITD thresholds [B] are presented. Circles represent TD, and squares represent sAPD groups. Note that the limit of y axis in panel B is 240 μs, i.e., the cut-off value (dashed vertical line in panel A).

Fifteen children from each group scored <120 μs, where 120 μs is the highest threshold obtained for ITD measurements in naive adult listeners (Ortiz & Wright, 2009). A further three children from each group scored >120 and <240 μs. However,

10 children, three from the TD and seven from the sAPD group, scored above 240 μs. As seen in the histogram seven children from the sAPD group scored above 960 μs, but only one child did so in the TD group. Adaptive tracking of participants whose data were indicated as outliers in SPSS (IBM Corporation, NY) 'Explore' function, i.e., ITD values >240 μs were inspected. This was done to understand if such extreme values arose due to a true underlying ITD discrimination problem, or because children did not understand the task. Examples of good and bad tracking are shown in Figure 8-6. Data of children whose tracking indicated that either they were not paying attention to the task, or did not understand the task, were excluded from further analysis.

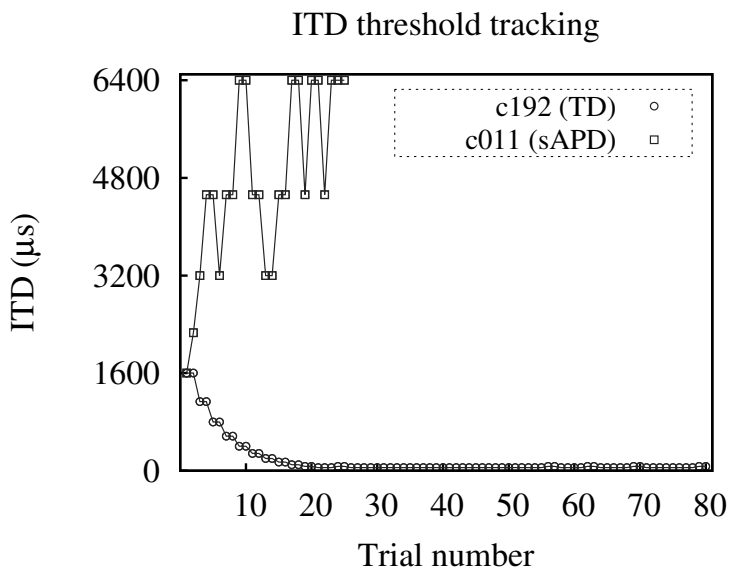

Figure 8-6: Threshold tracking in the ITD task for two participants, one from each group, demonstrate good and bad tracking. The experiment starts at 1600 μs and successive steps are decreased/increased on a geometric scale. The participant from the sAPD group clearly shows poor threshold tracking because the threshold increases to a very large ITD. The participant from the TD group has good tracking that decreases to a small ITD.

Figure 8-5B plots data from children that were not identified as outliers. There

were 18 participants in each group after rejecting outliers. An independent sample t-test showed no difference between TD (Mean = 88.03±23.81 μs) and sAPD (Mean = 88.16±19.70 μs) groups (t[34] = -0.01, p = 0.993). This may suggest that the ITD thresholds of both groups, measured using BBN, are similar, and corroborates results obtained in the free-field localization task.

8.3.3 Spatial Release from Masking

Raw HINT SNR scores were first converted to 'adult equivalent SNR' as per the HINT manual. These SNR scores are plotted in Figure 8-7A. These scores indicate the SNR required to obtain 50% correct speech reception scores for speech presented at 65 dBA SPL. A regression analysis with age as the independent variable and HINT score at 0° as the dependent variable was conducted to investigate the effect of age. Results indicated no systematic trend in HINT score as a function of age for both TD (β = 0.14, t[17] = 1.09, p = 0.291) and sAPD (β = 0.16, t[23] = 0.84, p = 0.408) groups. Note that one child from the TD group did not complete HINT measure due to time constraints. Visual inspection of the data in Figure 8-7A for SNR scores at 0° azimuth show that children in the sAPD group have slightly lower speech-in-noise perception compared to the TD group. This difference appears to be due to a few poor performers. A two-way RM-ANOVA with azimuth and group as independent variables, and HINT SNR scores as the dependent variable did not show any group (azimuth X group) interaction (F[2,88] = 2.16, p = 0.121, $\eta^2_{Partial}$ = 0.05). However, there was a significant main effect of azimuth (F[2,88] = 131.72, p<0.001, $\eta^2_{Partial}$ = 0.75), suggesting that when data were collapsed across groups, there was a significant difference in speech perception across the three azimuths.

Post-hoc tests with data collapsed across groups, interpreted with FDR corrections, showed a significant reduction in SNR required for 50% correct response at both

90° (MD = 5.21, $CI_{95\%}$ = ± 0.74 dB, $t[45] = 17.12$, $p<0.001$) and 270° (MD = 4.05, $CI_{95\%}$ = ± 0.85 dB, $t[45] = 12.14$, $p<0.001$) azimuths compared to 0° azimuth. This result suggests a significant release from masking, and the respective mean differences show the amount of release in masking in dB (Figure 8-7B).

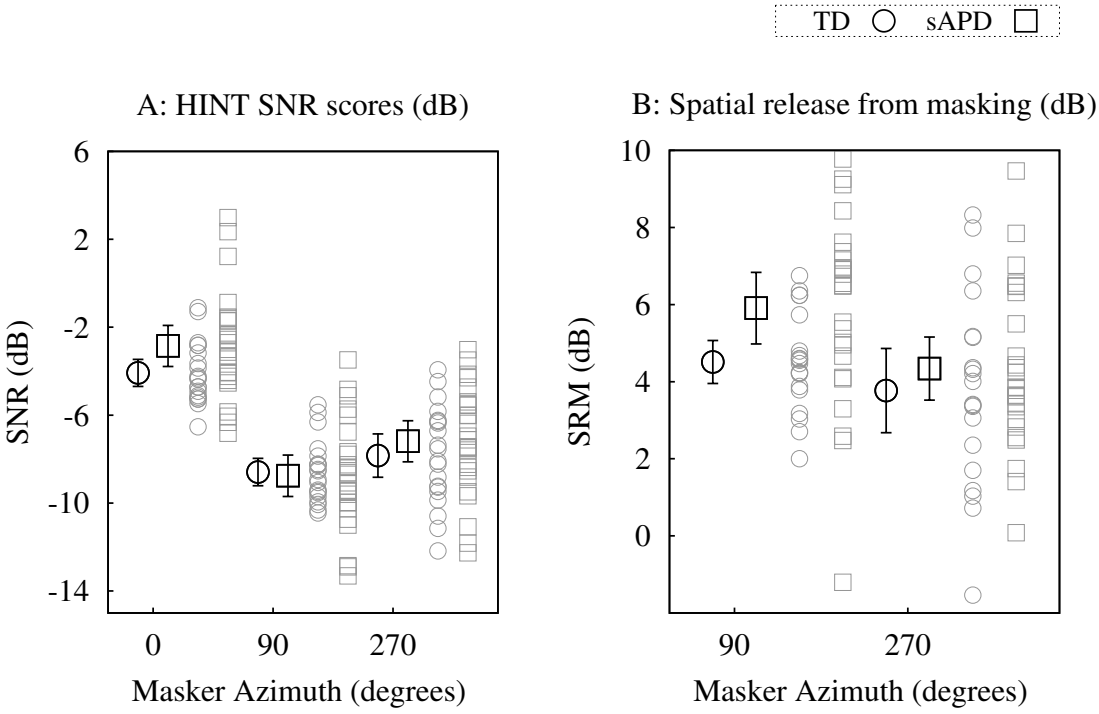

Figure 8-7: Plot A shows HINT SNR scores (dB) plotted as a function of masker azimuth (degrees). A derived metric from Figure 7A, SRM (dB), is plotted panel B or 90° (right ear) and 270° (left ear). In both plots, group means are indicated by black symbols and individual data by grey symbols. Circles in both plots represent the TD group and squares represent the sAPD group.

Lack of azimuth X group interaction indicates that SRM was not different across the two groups, corroborating results of other two binaural measures (localization and lateralization). Separate SRM scores were obtained for 90° and 270° azimuths by subtracting their respective SNR score from the SNR score obtained for 0° azimuth. Interestingly, SRM scores obtained for 90° and 270° were also significantly different

(MD = 1.21, $CI_{95\%} = \pm$ 0.73 dB, $t[45] = 3.30$, $p = 0.002$). This result shows that SRM was larger for 90° azimuth, which was always the right ear in every participant in the experiment, possibly reflecting right ear dominance.

8.4 Discussion

8.4.1 Localization-in-noise

The goal of this study was to better understand binaural hearing, pertaining to localization in children suspected with APD. Three different measures were used for this purpose: sound field localization-in-noise, lateralization assay to measure ITD, and SRM. Results of all three measures show that, despite numerically smaller performance scores in the sAPD group, they do not differ significantly from children in the TD group. Findings of the present study are thus contrary to reports of working groups of audiology professional bodies that suggest localization/lateralization can be one of the auditory processes affected in children with APD (AAA, 2010; ASHA, 2005; Bamiou, Musiek, & Luxon, 2001; Bellis, 2003). One reason that could have led to the inclusion of localization/lateralization in the list of affected processes in APD may be that, localization and lateralization are a part of central auditory processes, including auditory discrimination, pattern recognition, temporal processing, dichotic listening, and listening with degraded acoustic signals, that are required for normal listening (AAA, 2010; ASHA, 2005). Perhaps, localization difficulties are included in the definition of APD as part of a generic central auditory dysfunction (AAA, 2010). However, results of the current study suggests that such a deficit is not prevalent in children with listening difficulties.

With the exception of two unpublished theses (Wakeham, 2008; Zakaria, 2007), there are no studies that have investigated localization or localization-in-noise in

children with APD. Although both studies suggest that localization may in fact be affected in APD, to varying degrees, there is no clear consensus. Wakeham (2008) suggested that the differences observed between his TD and APD groups were sub-clinical due to considerable overlap in performance between the two groups. He also suggested that such subtle differences may not cause any localization difficulties in real life. Zakaria (2007) found significantly poorer localization in the F/B and U/D dimension in children with APD. He also found atypical binaural interaction using post auricular muscle response (PAMR), BMLD and ITD discrimination. Specific results and conclusions of Zakaria (2007) and Wakeham (2008) are unknown because both of these reports are unpublished, so, further comparisons between the findings of these two studies and current data is not possible.

Although data on localization in APD is sparse, several tests have been developed and are in use, to test the binaural system as a whole. These tests use either speech or non-speech stimuli dichotically or diotically to test the ability of the auditory system to integrate and/or fuse signals to form a coherent auditory image (Bellis, 2003). Examples of such tests are the SSW (Katz, 1998), binaural fusion test (Ivey, 1969), dichotic digits test (Musiek, 1983), and BMLD (Hall & Grose, 1993; Moore, Hutchings, & Meyer, 1991). Indeed, these tests are routinely used to identify children with auditory processing difficulties. Although there is no gold standard test to compare the results of these tests, at least some have been shown to be sensitive in identifying known brain lesions that cause auditory processing disorders (Katz & Smith, 1991; Musiek, Gollegly, Kibbe, & Verkest-Lenz, 1991). Objective measures such as the binaural interaction component (BIC) derived from auditory brainstem response have also been shown to be sensitive to subtle deficits in binaural signal processing in the auditory system (Delb, Strauss, Hohenberg, & Plinkert, 2003; Gopal & Pierel, 1999). Results of the present study suggest that while global binaural processing

may be affected in some children with APD, this may not necessarily translate to impaired localization ability. Even if children diagnosed as sAPD perform poorer than TD children, as suggested by Wakeham (2008), such differences may be sub-clinical and may not significantly impact day-to-day listening.

A question may arise as to why localization deficits may not be exhibited in children in whom binaural processing is thought to be affected. The answer to this probably lies in the number of processes a typical speech based binaural test, such as SSW, might tap. Many investigators suggest that attention and memory are intertwined with all auditory processes, consequently, the outcome of all auditory tests will have some variability due to the involvement of attention and cognition (Dawes & Bishop, 2009; Moore, Ferguson, Edmondson-Jones, Ratib, & Riley, 2010; Musiek, Bellis, & Chermak, 2005). For instance, Moore et al. (2010) studied a large sample ($n = 1469$) of randomly chosen children between 6 and 11 years of age with a variety of auditory processing tasks. Their results suggested that, in children who performed poorly in auditory tasks, attention and cognition scores best predicted their listening abilities. However, the amount of variability explained by attention, cognition and language may vary across different tests. The localization-in-noise assay in the present study used a speech token as target, but children were only required to identify the direction from which the speech sound emanated. On the other hand, dichotic tests like SSW involve listening to four words (two overlapping) and repeating them in the correct sequence. This process can be thought to involve, attending to all four words, storing them in temporary/working memory, retrieving them, and repeating them in sequence. Language skills further complicate task difficulty; children with poor language skills may fail such tests despite good auditory skills (Allen & Allan, 2014; Moore, Rosen, Bamiou, Campbell, & Sirimanna, 2013; Rosen, 2005).

The non-speech BMLD test on the other hand has been shown to be similar across APD and control groups (Cameron et al., 2006). BMLD is thought to test lower brainstem structures, while, SSW and other dichotic tests clearly involve higher order processing (Bellis, 2003). Due to such additional complexities involved in speech based binaural processing tests, poor performers may include children who do not have specific deficits pertaining to binaural signal processing, but rather experience other non-sensory deficits (Moore et al., 2010; Moore & Hunter, 2013). Therefore, an increased number of children may be identified as APD who may or may not have deficits in binaural processing (Wilson, Heine, & Harvey, 2004). In contrast, localization and lateralization assays in the current study used a rather simple task, involving perhaps non-sensory factors to a lesser degree. Considering SRM is obtained by comparison of speech-in-noise performance across three different conditions (repeated measures), non-sensory factors that arise due to the use of speech material may cancel out across spatial conditions (90° and 270°). Also, speech based dichotic tests have been reported to be sensitive to deficits in information transfer from left to right hemisphere (via corpus callosum), which may indicate a deficit unrelated to sound localization (Musiek et al., 1991). Further, localization errors of children who failed the SSW (12/26) performed as part of the current APD test battery, were compared with children who passed the SSW (14/26). Children in both groups performed at equal levels in all binaural hearing assays in this study. This further emphasizes that difficulties in binaural hearing, as measured by standard APD tests, do not necessarily indicate difficulties in localization.

8.4.2 Lateralization

There were no group differences in ITD threshold between the two groups. However, the results of ITD from the present study must be handled with caution due to a methodological caveat. Due to a software limitation, the smallest ITD threshold

value attainable was 60.34 μs. Larger proportion of children (43%) in the TD group obtained this threshold value compared to children in the sAPD group (12%). It is possible that children in the TD group could have scored better if the limits of our instrumentation were reduced further, which could have differentiated the two groups. Mean ITD threshold values obtained here for both groups are larger than those reported for children by Van Deun et al. (2009). However, considerable methodological differences exist between the present study and Van Deun et al. (2009). For instance, Van Deun et al. (2009) presented a reference signal in the mid-line and listeners were asked to judge the position of the second (test) stimulus (with different ITD) relative to the reference signal. In the present study, the reference was not fixed at mid-line. It is possible that the larger uncertainty due to a reference that was not fixed could have made it more difficult to identify the change in ITD. This difference in method could have led to higher ITD discrimination thresholds in the present study. The ceiling effect described above, observed as a result of software limitation, could also have inflated ITD threshold values in both groups.

Nevertheless, the motive of this study was to compare ITD thresholds between TD and sAPD groups. To this end, excluding the outliers, both groups performed at equal levels. However, the outliers cannot be wholely disregarded. It is interesting to note that more children (1 TD vs. 7 sAPD) in the sAPD group obtained ITD thresholds greater than 960 μs. For instance, two children in the sAPD group obtained thresholds greater than 5000 μs. Such high ITD thresholds are not found even in cochlear implant users (Laback, Pok, Baumgartner, Deutsch, & Schmid, 2004). Thus, an impairment in sAPD children's binaural hearing mechanism is probably not the cause of such high thresholds. Instead, inattention, fatigue or inability to follow task instructions could have led to such poor thresholds. Indeed, the inability to follow instructions is a common complaint in APD (Chermak, Somers, & Seikel, 1998). This is evident

in threshold tracking as seen in an example from a child in the sAPD group (Figure 8-6). Given the complexity of the task, perhaps more children in the sAPD group found it difficult to follow task instructions.

8.4.3 Spatial release from masking

SRM was similar in both groups. The amount of SRM obtained in the present study is slightly lower than the ∼10 dB SRM obtained for younger TD children (4.5 year olds) by Garadat and Litovsky (2007). Again, it should be noted that considerable methodological differences exist between the two studies. Garadat and Litovsky (2007) used a more child friendly test tool with inclusion of graphics, whereas the present study did not optimize the HINT protocol for use with graphics. The HINT used here requires children to repeat the entire sentence in order to be judged correct or wrong. Repeating whole sentences is more difficult and more errors can be expected compared to only repeating words as in Garadat and Litovsky (2007). Such differences may have restricted the SRM that could be achieved in the present study. An interesting observation in the SRM results is that, on visual examination of Figure 8-7B, children in the sAPD group appear to have benefited more than the TD group from the spatial separation of speech and masker, although this difference was not significant. This is in contrast to the findings of Cameron et al. (2006), who reported a significantly reduced SRM in children with APD. Their control group achieved an SRM of 10 dB, while the present study achieved a maximum of only 4.5 dB for the 90° azimuth condition. Their APD group on the other hand achieved an SRM of only 3.7 dB, while in the present study, the sAPD group achieved as much as 5.9 dB in the 90° azimuth condition. While Cameron et al. (2006) used a specialized test for spatial release from masking, the HINT is primarily a speech-in-noise reception test and thus lacks the sophistication of LiSN to obtain SRM. Nevertheless, based on the large effect size of the Cameron et al. (2006) study, if the sAPD group in the

current study indeed had poor SRM, it should have been observable in either measure.

One critical factor that could have differentiated SRM between groups based on SRM in the Cameron et al. (2006) study and not the current study, could be the difference in maskers. LiSN uses distracter sentences (meaningful speech) as maskers, while the current study used speech-spectrum noise. Competing speech is known to cause larger informational masking, compared to energetic masking caused by speech-shaped random noise (Brungart, Simpson, Ericson, & Scott, 2001). While children in general are more prone to informational masking (Hall, Buss, & Grose, 2005; Oh, Wightman, & Lutfi, 2001; Wightman, Callahan, Lutfi, Kistler, & Oh, 2003), and distraction (Allen & Wightman, 1994; Lutfi, Kistler, Oh, Wightman, & Callahan, 2003), it is possible that children with APD are even more vulnerable. Therefore, the type of masking release obtained in the present study and that of Cameron et al. (2006) does not strictly measure the same underlying mechanisms. Perhaps children in the sAPD group are genuinely able to reap similar benefits from spatial separation of speech and noise, provided the noise only causes energetic masking. However, as evidenced from the LiSN test (Cameron & Dillon, 2008; Cameron et al., 2006), children with APD may benefit less from spatial separation when the masker causes informational masking. Further studies that investigate SRM in both energetic and informational maskers may provide evidence for this hypothesis.

8.4.4 General discussion

It is well known that APD is characterized by heterogeneity in listening difficulties, and in test battery outcomes. Different children fail different tests within a battery. There is no 'pure' APD where only one modality or a specific auditory processing ability is affected. 'APD' is thus an umbrella term encompassing a wide variety of deficits ranging from temporal processing, to attention (Dawes & Bishop, 2009).

Therefore, for investigation of specific auditory modality deficits, selection of children based on an APD test battery may not be very useful, as much as they are clinically useful in APD diagnosis. The current study included both children diagnosed as APD and non-APD to mitigate pitfalls related to excluding children based on the outcome of an APD test battery (Allen & Allan, 2014). Perhaps, previous studies that show significant group differences in localization used stricter criteria in including APD children, or children who were severely impaired (Zakaria, 2007).

Asymmetric or unilateral conductive hearing loss has been shown to alter short-term brain plasticity in the auditory system that persists even after the peripheral hearing loss has resolved, affecting binaural hearing (Moore, Hartley, & Hogan, 2003). Perhaps investigating the localization abilities of children with a history of known binaural processing deficits and a history of otitis media may provide insights into the relationship between binaural hearing and localization in APD. Evidence for impaired binaural processing in children with a history of otitis media comes from impairments in BMLD, a non-speech diotic test (Hall & Grose, 1993; Moore et al., 1991).

It is also possible that the present study was unable to detect an underlying deficit in localization-in-noise performance in children with sAPD. Two reasons for such an inability can be considered: sample size and sensitivity of the measure. Sample size in the previous two studies [Zakaria (2007): 20 TD, 15 APD; Wakeham (2008): 24 TD, 24 sAPD] that report significant differences between the TD and sAPD groups in localization are comparable to the present study (21 TD, 26 sAPD). Therefore, sample size may not be a factor contributing to the non-significant differences between TD and sAPD groups in the current study. In addition, post-hoc power analysis using G*Power software (with β/α ratio = 1; Faul, Erdfelder, Lang, & Buchner, 2007) with combined means and standard deviations (across SNRs) for FBpc and Lscat shows

a moderate power of 0.56 for both measures. Another possibility is that the metrics used to quantify localization was not sensitive enough to identify subtle differences in localization abilities between the two groups.

However, that FBpc, Lscat, ITD discrimination, and SRM were all same between groups suggests that the two groups are genuinely not different in their localization abilities. Clearly, more studies are needed to reconcile the findings of the present study, and establish if localization-in-noise is indeed affected in children with APD. However, it is clear that while some children may have difficulties in localization, due to the heterogeneity of the disorder, it is not prevalent across APD. Identification of children based on a hierarchal model suggested by Dillon (2012) may be more appropriate to disambiguate APD, and identify those children with specific auditory processing difficulties. Dillon (2012) suggested using a master test to decide what auditory process is affected, and follow-up with more detailed tests that are specific to the one affected auditory process. For example, children who fail the binaural component of the SSW may be tested with the LiSN, localization tests, and BMLD to establish the problem domain. This method may help identify the underlying problem, facilitate treatment, and be more useful than labeling someone as APD. Future research in APD should probably focus on fragmenting APD into separate entities that show a specific tendency to one type of listening difficulty, such as the spatial processing disorder identified by Cameron et al. (2006).

8.5 Conclusion

Localization-in-noise, ITD discrimination, and spatial release from masking were compared in children with listening difficulties (both APD and non-APD) and TD children in the present study. Results indicate that children with listening difficulties do not

differ significantly from TD children on all three assays. These findings contradict two previous unpublished reports on localization in APD, probably due to methodological differences, and inherent heterogeneity of the disorder. While some children may indeed have difficulties with localization-in-noise, it is unclear if these subtle difficulties will make any difference in day-to-day listening (Wakeham, 2008). Further investigations are warranted to reconcile contradicting results on the localization function in APD.

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Chapter 9

Summary and Concluding Remarks

9.1 Summary

9.1.1 General Summary

The general aim of this work can be divided into two parts; (1) to investigate physiological irregularities in the peripheral and brainstem auditory mechanisms in children with APD, (2) to understand the role of spatial hearing in children with APD. Both aims pertained to auditory noise reduction mechanisms that may influence speech perception in noise, the prime complaint in children with APD. These mechanisms are widely reported to aid normal listening individuals in understanding speech in noisy environments, but have been scantily studied in the children with APD.

Due to the heterogeneity associated with APD, it is not surprising that a single physiological process or an anatomical site cannot be isolated as the reason for the disorder across all children diagnosed with APD. Nevertheless, physiological irregularities in the brainstem, and cortical processing of auditory signals in children with listening difficulties have been reported recently (e.g., Allen & Allan, 2014; Muchnik et al., 2004), which is encouraging for future research. Understanding the underlying physiological irregularities may pave the way for differential diagnosis, and disam-

biguation of the term APD itself (Dillon, 2012).

To this end, three auditory noise reduction mechanisms (cochlear tuning, efferent function, and spatial hearing) were investigated in children with listening difficulties (sAPD group), and their results were compared with typically developing (TD) children who did not report any listening difficulties. More specifically, Chapter-5 reports an investigation of cochlear tuning using a physiological measure based on stimulus frequency otoacoustic emissions (SFOAEs) and their relationship to medial olivocochlear (MOC) functioning. The specific motives for this study were that: (1) subtle deficits in cochlear tuning go undetected in conventional audiological screening, and (2) peripheral auditory mechanisms have not been investigated in great detail in children suspected with APD. Considering that MOC function is crucial for the proper development of cochlear tuning, the relationship between tuning and MOC function was also probed. Chapter 6 reports findings on the working and strength of the binaural MOC reflex obtained using a forward masked click evoked OAE (CEOAE) assay. Motivation for this study stems from the fact that the binaural MOC reflex will almost always be stimulated in real life, and that contralateral MOC function, as typically studied, may not be a good proxy for either the ipsilateral or binaural MOC reflex. Further, contradicting results on the relative strength of MOC in the sAPD group was observed between Chapters 5 and 6 led to a comparison of the MOC strength obtained using three different OAE assays (SFOAE, CEOAE, and distortion product OAE [DPOAE]) in Chapter 7. Finally, Chapter 8 reports an investigation of spatial hearing using three assays: localization-in-noise, spatial release from masking (SRM), and interaural time difference (ITD) thresholds.

An 'optimization' (stimulus and instrumentation) phase preceded the 'APD study' phase described above. Three studies were conducted in the optimization phase in

normal listening adults and children. Chapter 2 describes an investigation into the previously reported enhancement in MOC sensitivity to 100 Hz amplitude modulation. The motive behind this study was to use a 100 Hz modulated MOC elicitor instead of an unmodulated elicitor to improve the effect size of the MOC inhibition of OAEs. The study described in Chapter 3 aimed to find the optimal click stimulus presentation rate for eliciting CEOAEs without activating the ipsilateral MOC reflex. Although it is well known that faster click presentation rates evoke MOC activity, the rate at which the ipsilateral MOC is activated in a typical MOC assay remained elusive. Finally, localization-in-noise ability of TD children was studied and described in Chapter 4. The motive for this study evolved from the paucity of data on localization-in-noise abilities of young children.

9.1.2 Summary of Findings

Optimization Phase Studies

Results from studies in the optimization phase (Chapter 2-4) have improved our understanding of some of the physiological properties of the MOC, and have revealed localization-in-noise abilities in children and adults in the front/back and lateral domains.

First, in Chapter 2 the replicability of previously reported (Maison, Micheyl, & Collet, 1999) improvement in MOC inhibition of OAEs was investigated using broadband noise (BBN) modulated at 100 Hz. This property of the MOC was studied using two different OAE-types (SFOAE and tone-burst OAE [TBOAE]) and frequencies spanning two octaves. Results of this study indicate that MOC activity may not be enhanced at 100 Hz, contradicting the findings of Maison et al. (1999) but corroborating Backus (2005). Based on the MOC time constants, it appears that 100 Hz is too fast for the MOC to follow. Low level periods in a modulated elicitor appear to reduce its effectiveness in eliciting MOC activity. Therefore in this work, subsequent stud-

ies on MOC function in children suspected with APD did not use modulated elicitors.

In Chapter 3 a search for the optimal click stimulus presentation rate for use in MOC assays was carried out using a forward masking method that emulated typical MOC assays (click stimulus in the ipsilateral ear and MOC elicitor in the contralateral ear). Results indicated that click rates as low as 31.25 Hz evoke significant MOC activity and contaminate contralateral MOC inhibition of CEOAEs with ipsilateral and binaural MOC activity. This result has implications in both clinical and research settings when investigating MOC function using CEOAEs and contralateral noise elicitors. Due to temporal energy integration in the MOC, 50 Hz click rate the typically used will certainly elicit the ipsilateral MOC response. Therefore rates $\leq$25 Hz appear ideal for use in MOC assays.

The goals of Chapter 4 were two fold: (1) to investigate if the localization-in-noise ability of children (7-17 years) is adult-like for two different noise maskers (uniform and random broadband noise [BBN] and speech-babble [SB]), and (2) to investigate the relationship between front/back localization ability and MOC strength. Results indicated that while children are able to grossly differentiate sounds coming from front and back as well as adults in quiet, and amidst an energetic masker (BBN), they made significantly more errors in the presence of the informational masker speech-babble. Their responses were also less consistent. These findings suggest that, despite maturation of the required neuronal circuitry to localize sounds in noise, non-auditory factors may prevent children from localizing sounds accurately amidst an informational masker. Further, no correlation between MOC strength and localization-in-noise was found in both adults and children. This finding indicates that MOC activity is involved to a lesser degree in unmasking azimuthal cues from noise as compared to elevation cues (Andéol et al., 2011). Finally, binaural MOC interaction was signifi-

cantly different between adults and children, despite similar inhibition of OAEs.

Overall, studies in the optimization phase identified some basic temporal aspects of MOC physiology and recommended optimal parameters for recording CEOAEs in MOC assays that are relevant for both research and clinical use. It was also revealed that despite mature localization abilities in children as young as 5 years Van Deun et al. (2009), localization-in-noise abilities appear to develop on a protracted scale for informational maskers, which is presumably due to immaturity of non-auditory factors.

APD Studies

The study described in Chapter 5 investigated the role of cochlear tuning, and its inter-relationship with MOC function in children with sAPD. Results indicated that cochlear tuning is sharper in the sAPD group when compared to TD children. This finding was contrary to our hypothesis that children in the sAPD group may have broader tuning. However, these findings suggest that many children in the sAPD group could be more vulnerable to forward masking that may influence their temporal resolution. Further, reduced MOC control on the cochlea, and an inverse relationship between MOC strength and change in tuning suggests differential cochlear and MOC function in children in the sAPD group.

Chapter 6 investigated the role of binaural MOC function and interaction in children with sAPD. Previous studies in the APD literature have only investigated the contralateral MOC pathway, so the role of ipsilateral and binaural pathways were largely unknown. In addition, the results of Chapter 4 suggested a different binaural interaction of the MOC between TD children and adults. Although the implications of the binaural interaction of the MOC are not very clear, it was probed in this study

to investigate the existence of potential deficits in the study population. Results suggested that MOC function and binaural interaction in both groups were similar, which conflicted with the initial findings of Chapter 5. A behavioral measure of binaural interaction [Binaural Re-synthesis Test (Ivey, 1969)] did not show any significant difference between the two groups.

Contradicting findings were found in Chapters 5 and 6; SFOAE based MOC assay suggested reduced MOC function in children with APD (Chapter 5) while the CEOAE based assay did not show such group differences (Chapter 6). Therefore a study was designed (Chapter 7) to reconcile the results of these conflicting studies. In this study, strength of the MOC reflex in children with sAPD was assayed using three different OAEs and compared with TD children. Neither CEOAE nor DPOAE measures in the two groups showed any significant difference in MOC strength. Although there was a significant difference in the SFOAE assay, the significance was lost due to corrections for multiple comparisons. It is still unclear if MOC strength is reduced in children with sAPD.

Finally, Chapter 8 details the investigation of localization-in-noise abilities of children with sAPD. Various professional bodies (e.g., American Academy of Audiology [AAA], 2010) have suggested that localization is one of the affected processes in children suspected with APD, yet there are few published data. Front/back and lateral angle localization was obtained in two different noise maskers (broadband and speech-babble) in children with sAPD. Results of this study indicate that localization abilities of children in the sAPD group are not significantly different from TD children, contrary to the supposition of professional bodies.

Revisiting the conceptual model introduced in Chapter 1, the present findings

suggest altering it slightly for children in the sAPD group. As seen in Figure 9-1, it is now clear that children in the sAPD group have sharper than typical cochlear tuning. This may lead to reduced temporal resolution and increased forward masking, which may in turn affect their speech perception in noise.

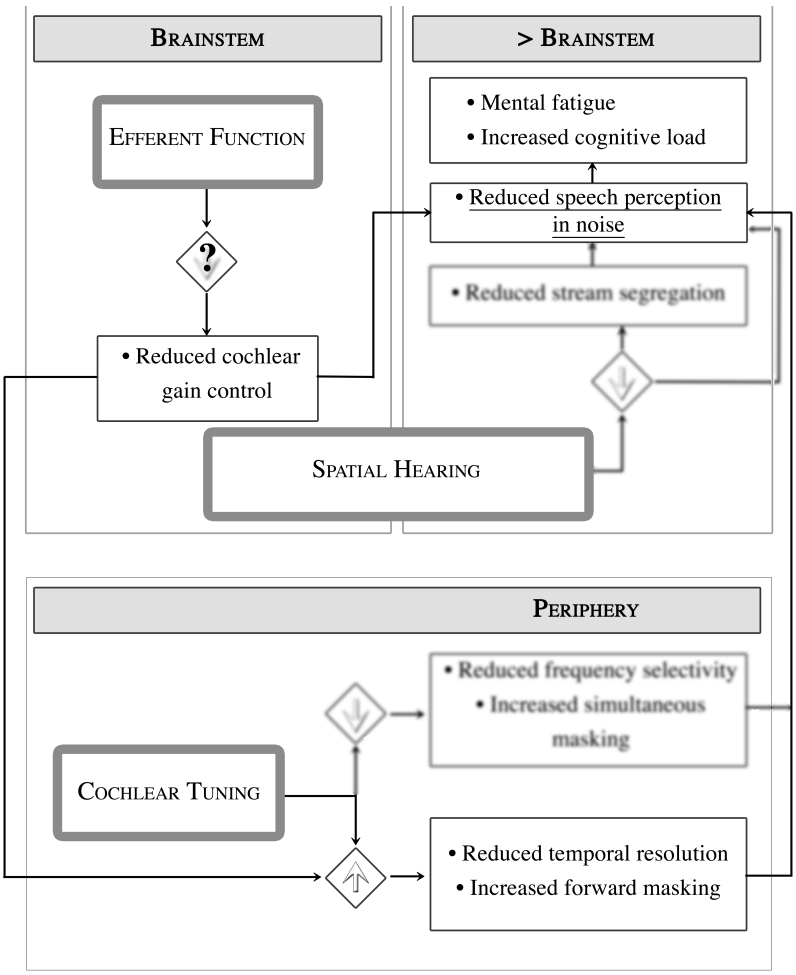

Figure 9-1: A conceptual model involving the three noise reduction mechanisms, grouped under their respective anatomical positions. Filled thin black arrows connect processes/mechanisms to their further consequential outcomes. Unfilled grey arrows inside decision boxes indicate sharp (up arrow) or broad (down arrow) tuning, reduced MOC function (down arrow), and reduced localization-in-noise (down arrow). Note that only the processes/mechanisms within thick grey boxes were investigated in this work, their outcomes are inferred based on empirical evidence from previous studies. Blurred boxes indicate that the current findings rule out the possibility of those outcomes.

Localization-in-noise, spatial release from masking and ITD sensitivity does not appear to be affected in children with sAPD, so these abilities may not contribute to their speech perception problems. Finally, although efferent function does not appear to be affected in children with sAPD at the group level, many children in the sAPD group do appear to have reduced MOC functioning. This is evident from the variability in results across OAE types, and the numerically smaller MOC inhibition of OAEs in the sAPD group. This finding portrays the heterogeneity in auditory problems associated with APD.

9.2 Implications

The findings recorded in Chapter 2 indicate that the MOC is not as sensitive to 100 Hz modulation as was previously thought, and illustrates that the MOC integrates energy temporally. This finding has extended our understanding of the temporal properties of the MOC, and may have implications in design of future research and theoretical modeling of MOC function.

The findings described in Chapter 3 have direct clinical and research implications. Clinically, audiologists will need to be more aware of the contributions of ipsilateral, contralateral, and binaural MOC effects are in part dependent on click presentation rates. In future research, investigators will be able to control for activation of ipsilateral and binaural MOC activity by using lower click presentation rates. Further, the correction factors for higher click presentation rates will also aid clinicians and researchers alike if they are unable to use slower rates, for example, with children.

The findings recorded in Chapter 4 provide evidence that maturation of the underlying auditory neuronal circuitry is sufficient to carry out complex tasks such as

speech localization amidst noise that causes energetic masking. However, maturation of non-auditory factors may play a role in protracted development of localization-in-noise amidst the informational masker speech babble. These findings also corroborate studies that show children are more prone to informational masking compared to adults (e.g., Hall, Buss, & Grose, 2005). This finding may have implications when advocating for acoustical considerations in school classroom settings. Performance equivalent to adults in localization amidst a broadband masker, suggests that children are as prone to the effects of energetic masking as adults, corroborating findings in previous spatial release from masking studies (e.g., Lovett, Kitterick, Huang, & Summerfield, 2012). These findings may have implications in developing spatial listening tests, and generating normative data for young children on localization-in-noise tasks. Implications of the difference in binaural interaction of the MOC between adults and children are unclear and therefore require further investigation.

Chapter 5 provides the first evidence of subtle differences in cochlear function and its links with MOC function between TD children and those with sAPD. These findings may have implications in the definition of APD itself. No previous studies had investigated the possible role of the cochlea in children suspected with APD (Bellis, 2003). These results show that deficits in children suspected with APD can include aberrant tuning within the cochlea. Upon further validation of the present findings by other investigators, future iterations of an APD definition may incorporate peripheral mechanisms in their list of deficits. Already, the change in central processing due to middle-ear effusion and related plasticity in children, has been attributed to the peripheral origin of APD (Moore, Hartley, & Hogan, 2003). The difference in the effect of MOC activation on cochlear tuning between the two groups also requires further validation. The current results provide impetus to studies that may investigate links between MOC and cochlear function.

Chapter 6 details the first study of binaural MOC function and interaction in children with sAPD. No significant differences in MOC function between children with sAPD and TD children were found. Considering Chapter 5 shows a significant difference in MOC function between sAPD and TD children, findings of this study complicate the interpretation of MOC function of the sAPD group. However, the method used in the study was successful in obtaining binaural MOC inhibition of CEOAEs in young children in a reasonable amount of time ($\sim$25 minutes). Studying binaural MOC may provide a better indication of MOC function in real life. Although first reported almost 20 years ago by Berlin, Hood, Hurley, Wen, and Kemp (1995), only a handful of studies have investigated binaural MOC activation. This is probably due to the complexities involved in separating signal and elicitor in the ear-canal. The method used in the present study can be easily adapted to clinical OAE instruments. The findings and methods of this study may therefore have both clinical and research implications for future investigations on binaural MOC function.

Chapter 7 describes a comprehensive study of MOC strength in sAPD participants using three different OAEs (SFOAE, CEOAE, and DPOAE with components unmixed) but the results were equivocal. It is not yet clear if MOC function is indeed affected in children with APD. Implications of these results may help disambiguate APD as an umbrella term and identify children with specific deficits. For instance, identifying children with reduced MOC function may help in developing targeted treatment regimens. Considering MOC is amenable to training, improvement in MOC strength may parallel improvements in speech perception in noise (de Boer & Thornton, 2008; Veuillet, Magnan, Ecalle, Thai-Van, & Collet, 2007).

The study in Chapter 8 showed that children with sAPD, in general, may not have

deficits in localization-in-noise, as suggested in the reports of various professional bodies (e.g., AAA, 2010). In addition, as speculated in Chapter 5, longer filter ringing in children suspected with APD does not seem to affect their gross localization ability, as measured in Chapter 8. Investigating the relationship between cochlear tuning and ITD in the same sample might provide further insights. Considering the findings of the present study contradicts two unpublished reports on the localization abilities of children with sAPD (Wakeham, 2008; Zakaria, 2007) it calls for further investigation. However, if localization-in-noise was indeed unaffected in a significant number of children with sAPD, then identifying children with such deficits and prescribing targeted treatments may help children with genuine localization deficits, similar to the implications of results from Chapter 7.

Overall, the results of four studies on children with sAPD corroborate literature reporting large variability associated with sAPD. The spread of sAPD data in all four studies was large and overlapped with the TD group, suggesting that not all children with listening problems have similar deficits in the auditory system. Statistical comparisons of data with such large variability are less likely to show significant differences across groups. However, heterogeneity within the sAPD group does not negate the fact that these children may have genuine listening difficulties. Non-significant results only means that the deficit under question is not homogeneous across the entire sAPD cohort. Some reasons for this heterogeneity may be the inclusion of a large number of symptoms, and consequently, diagnostic tests for the diagnosis of APD. This also leads to large variability in findings across studies. Therefore, investigating physiological mechanisms in children with auditory problems that are homogeneous across the group would better inform about the underlying aberrations. This will also lead to a reduction of mis-match across studies, and will facilitate systematic reviews in the future. Currently, there is only one systematic review available in the

APD literature that reviews treatment methods (Fey et al., 2011). No studies have yet systematically reviewed methods used in APD diagnosis. Further, the present findings, although non-significant in some cases, call for a better definition of APD itself, or a fragmentation of APD into several deficit specific disorders, which may help in achieving a diagnosis and that can lead to effective treatment, as suggested by Dillon (2012).

9.3 Strengths

- The present work aimed to investigate potential physiological mechanisms that may be associated with the most commonly reported problem in children with APD: speech understanding in noise. Objective methods were used, except in the spatial hearing studies. Unlike typical behavioral tasks that are used in clinical and research settings for APD testing, objective methods avoid non-auditory factors that often influence study results. The focus of this work was only on mechanisms that are thought to promote speech perception in adverse listening conditions. By keeping a narrow focus, we were able to use objective methods that are known to invoke responses from known anatomical regions along the auditory pathway. This aids in the interpretation of the results.

- The optimization phase allowed for the selection of ideal stimulus parameters and instrumentation for use in further studies. These parameters yielded robust OAEs while avoiding complications such as the middle-ear muscle reflex (MEMR). These parameters are easily transferable to both clinical and research settings for clinicians and investigators interested in studying the MOC using OAE assays. Consideration of these parameters in future studies will improve the quality of the OAEs obtained.

- Several steps were taken to prevent and identify the MEMR effects on OAEs.

First, only children with acoustic reflex thresholds higher than 70 dB HL were included in the screening stage. Later, offline tests were conducted to investigate subtle changes in the stimulus level in the ear-canal that may have indicated MEMR activation.

- The quality of OAEs obtained in this work can be considered high, consequently the MOC inhibition can also be considered to be of good quality. Quality of responses here refers to the size of the emission above the noise floor, or the signal-to-noise ratio (SNR). In the present work, a high (10 dB) SNR was set as the cut-off for response inclusion. This is uncommon for OAE-MOC studies in APD, but ensured that the findings minimized influence from the noise floor.

- Despite a high rejection rate in the sAPD group, the sample size was considerably larger than most OAE based MOC studies, and comparable with studies that report significant group difference between APD and TD children for MOC measures (e.g., Muchnik et al., 2004). Power calculation based on mean and standard deviations of Muchnik et al. (2004) indicated that a sample size of 15 in each group is required to achieve a power of 0.8. All studies in this work included more than 15 participants. Therefore, the power of all studies reported here for the MOC inhibition of OAEs can be considered reasonable, and the non-significant effects should not be related to the sample size.

- One problem that affects most MOC assays that do not use an interleaved elicitor presentation method is probe-drift. Level changes in OAEs due to probe-drift can mislead an investigator into thinking an OAE level reduction is due to MOC activation. The current study avoided this problem by using short duration (2, 2.5 or 8 s for SFOAE, CEOAE and DPOAE assays, respectively) sweep-blocks for interleaving the elicitor on and off. Unlike continuous elicitor presentation methods, interleaving the elicitor on/off minimizes the differential

effect of probe drifts.

- A normalized metric was used to quantify MOC mediated change in OAE level (re: baseline OAE level in no-elicitor condition). By obtaining a normalized metric, as recommended by Backus and Guinan (2007), the influence of individual differences in OAE levels on the MOC strength was ruled out.

- The use of three different OAE measures to reconcile contrasting findings from the present work, and also from the literature, provides a comprehensive view of the status of MOC function in children with sAPD.

- Two different maskers were used (broadband and speech-babble) in localization studies helped in identification of the protracted development of non-auditoy factors, and their influence on localization amidst speech-babble in TD, and sAPD children.

- The use of a diffuse masker source created a more real-life noise field, in addition to avoiding masker location related complexities in localization (Lorenzi, Gatehouse, & Lever, 1999).

9.4 Limitations and Alternate Methods

Several limitations of the work need to be acknowledged:

- The conceptual model introduced in Chapter 1 assumes that all the auditory noise reduction mechanisms investigated in this work pertain to speech perception in noise. While previous studies indicate that the mechanisms in question do influence speech-in-noise perception, the degree to which they aid speech-in-noise perception can be ascertained only with the use of appropriate test materials. Such a direct correlation was not done in this present work, instead

the focus was only on the investigation of the underlying mechanism. Speech-in-noise tests with low redundancy could be used for this purpose but it should be noted that the Hearing In Noise Test (HINT; Nilsson, Soli, & Sullivan, 1994), a sentence perception test, did not show any group differences between the sAPD and TD children included in this study.

- The focus of this work was the investigation of mechanisms that may aid speech perception in noisy environments, considering speech in noise is the prime complaint in children who are referred for APD testing. However, children with APD may also have other difficulties such as difficulty understanding rapid speech, following instructions, attention, academic difficulties, and difficulty following subtle prosodic changes in speech (AAA, 2010). These difficulties were not a focus of this work. It is possible that some children included in the sAPD group in this study do not have any speech-in-noise problems at all, but may have other auditory difficulties. Inclusion of such children, although suspected of having APD, may have led to non-significant group differences in the processes being studied. Inclusion of children with only speech-in-noise problems and/or analysis of subgroups of children with different APD profiles could have resulted in different outcomes. Although such a select study group may not represent the current definition of APD it may help in the targeted investigation of a breakdown in specific physiological mechanisms.

- All OAE-based studies in this work required a high signal-to-noise ratio of 9 dB or more to consider a response as above noise floor. While this is one of the strengths of this work, it also led to an increased rejection rate (see Chapter 5). Also, the rejection was disproportionate; more sAPD than TD participants were rejected from the study. This may indicate that children with sAPD have inherently higher noise levels than their age matched TD peers. Therefore the

methods used in this work, at least for the SFOAE phase measurement, are not very robust to noise related artifacts. Two reasons could have led to the higher rejection rate in the SFOAE assay: (1) SFOAE was completed first in most participants, and participants rejected from the SFOAE assay were not recalled for other OAE measures, therefore many children with poor SFOAEs did not participate in other OAE measures, (2) SFOAE measurement took the longest to complete (∼30 minutes), increasing the chance of participant related artifacts. SFOAE phase measurements are particularly sensitive to movement artifacts; because artificial changes in phase (between frequencies) even by a few degrees can render the phase data non-meaningful for obtaining reliable phase gradients and group delay. Measurement of phase in closely spaced frequencies (e.g., 4 Hz; the present study used 16 Hz) in discrete clusters is one option to avoid phase related complexities (Francis & Guinan, 2010). Another option is using more novel methods such as a SFOAE sweep measurement technique (Kalluri & Shera, 2013). However, both these measures have not yet been used with children and therefore the outcomes are yet to be ascertained.

- In consideration of time, OAEs from only one ear per participant were obtained in all studies in this work. Previous studies have indicated a functional asymmetry in MOC inhibition of OAEs, which is thought to be a manifestation of right ear dominance observed throughout the auditory system (Khalfa & Collet, 1996). This asymmetry is thought to be a part of typical listening ability and is reduced in individuals with listening difficulties (Veuillet et al., 2007). Obtaining MOC inhibition of OAEs from both ears could have added more information to the present work.

- Most children spent around two hours to complete the entire study. These two hours were in addition to the time taken for their APD diagnostic tests

(approximately 1 hour). Although most assays in this work are objective, and the order of tests were semi-randomized, fatigue may have had an effect in some children. Testing was completed in a single session in most participants due to a lack of participant willingness to attend two sessions. Conducting all studies spread across 2-3 sessions may have avoided fatigue. However, multiple visits would have significantly increased the time required to complete a given study, and may have led to increased participant drop-out.

- In Chapter 2, only one modulation frequency was studied. This was done to replicate a previous study's findings (Maison et al., 1999). More modulation frequencies could have been included in the study to obtain a complete perspective of the temporal characteristics of the MOC.

- Only one click level (55 dB peSPL) was investigated in Chapter 3, as the focus was on click rate. Considering that a 20.83 Hz click rate was used for 'test-clicks', the experiment took each participant ∼2.5 hours to complete. However, previous studies have indicated the effect of elicitor level on MOC inhibition of OAEs non-linear (Hood, Berlin, Hurley, Cecola, & Bell, 1996), therefore recommendations from this study can only be used where 55 dB peSPL clicks are used.

- In Chapter 7, the method used to separate DPOAE components, although promising, is based on signal processing assumptions. There is always a margin of error in separating the two components. Improved automated methods are required to objectively, and consistently separate DPOAE components.

- In Chapter 8, the interaural time difference (ITD) assay showed a prominent ceiling effect, and only one trial per participant was performed due to time constraints. Therefore results of this assay must be considered with caution.

9.5 Future Directions

Several questions have come to light from the findings of the current work and warrant further investigation. Also, some new results are reported that require further validation.

- Results of Chapter 2 suggest that the MOC is not especially sensitive to 100 Hz modulation, and that it integrates energy over time. Future studies may investigate the energy integration of the MOC in greater detail. Considering only 100 Hz modulation was evaluated in the current work, the effects of other modulation frequencies should also be investigated. Although, Backus (2005) investigated several modulation frequencies, his study only involved four participants. Validation in a larger sample is warranted.

- Results of Chapter 3 apply only to a 55 dB peSPL click stimulus. The present findings should be extended to other click levels (low to high). In addition, more click rates could be evaluated in order to determine a narrower range of optimal click presentation rate.

- Results from Chapter 4 suggest that MOC activity may not play a role in azimuthal plane localization, but from Andéol et al. (2011) it is understood that the MOC aids median plane localization. It is unknown if the same applies to children. The reflexive pathway of the MOC, typically studied using acoustic stimuli, is mature at term birth (Abdala, Mishra, & Garinis, 2013). Therefore, differences in MOC activation between adults and children may not arise due to the reflexive element of this pathway, rather from corticofugal influences, perhaps due to focused attention (de Boer & Thornton, 2007). Therefore, a MOC study that controls for attention while measuring localization and MOC inhibition of OAEs may throw light onto differences in MOC function in adults and children.

- Chapter 5 provides evidence for physiological irregularities at the peripheral level in children with sAPD. First, this finding must be validated. Next, the possible repercussions of such irregularities must be ascertained.

- The method used in the study in Chapter 6 shows promise for use with children and could be easily introduced into clinical OAE instruments. Future studies with a clinical focus and a wider range of disorders may aid in our understanding of the binaural MOC system. Further, functional asymmetry in the MOC may prove to be more informative when ipsilateral and contralateral MOC pathways are investigated separately, compared to studying only the contralateral pathways of the left and right ears.

- An improvement over the method from Chapter 7 could be an investigation of MOC function using all three OAE types, but in a homogeneous study group. For example, only with children who complain of speech-in-noise difficulties and fail speech-in-noise tests. This may provide a better indication of MOC function in children who only suffer from speech-in-noise deficits, and may also extend our understanding of the MOC.

- The results of Chapter 8 contradict two previous unpublished reports (Wakeham, 2008; Zakaria, 2007) on localization abilities of children with APD. Therefore further study is warranted to reconcile contradictory findings. Also, an investigation of localization abilities for sounds of varying elevations may provide more insight into the localization abilities of children with sAPD. Studies that investigate SRM in energetic, and informational maskers are warranted.

9.6 Concluding Remarks

Studies conducted during both the optimization phase and APD study phase have contributed to our understanding of some basic MOC functions. It is now clear that the MOC's time-constants prevent it from following 100 Hz amplitude modulation. Also, consideration of click stimulus presentation rates for MOC assays is essential to avoid ipsilateral and binaural MOC activation. The MOC may not play a role in localization-in-noise in the azimuthal plane.

Evidence for cochlear involvement in children with sAPD is perhaps the most important finding of this work. As stated in the introduction, this is one of the noise reduction mechanisms in the auditory system. Therefore, increased cochlear tuning may contribute to speech processing deficits in some children. This finding calls for, upon further validation, inclusion of the peripheral auditory system in the list of processes affected in APD. This has opened a new avenue to pursue for research in the APD domain. Studies that investigate other peripheral processes may further improve our understanding of peripheral contributions to APD. Results from other studies in the present work highlights the heterogeneity of deficits in children with APD. Nevertheless, unlike localization-in-noise, MOC function appears to be affected in at least some children with listening problems. Investigating MOC function or localization-in-noise in children with a homogeneous auditory deficit may be a better means to study the role of specific auditory processes in children with APD.

In general, based on the APD data, disambiguating the term 'APD' appears to be necessary. Also, fragmenting constituent deficits under the umbrella term 'APD' into process specific disorders may be useful. Although it is impossible to separate contributions of one auditory process from another, at least identifying a predominant deficit, and possibly a physiological reason behind the behavioral manifestation, may help in targeting treatment regimens that may help the child. It is thus necessary to continually search for potential 'biological-markers' of APD. Identification of biologi-

cal markers linked to specific auditory processing deficits will aid in the development of gold-standard tests.

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Appendices

Appendix A: Ethics approval notice

re-issued

Office of Research Ethics

The University of Western Ontario

[redacted]

Use of Human Subjects - Ethics Approval Notice

Principal Investigator: Dr. D. Purcell

Review Number: 17731E **Review Level:** Expedited

Review Date: January 12, 2011 **Approved Local # of Participants:** 180

Protocol Title: Role of Otoacoustic emission generation mechanisms and medial olivo-cochlear bundle in hearing: comparing children with and without auditory processing disorders using Otoacoustic emissions.

Department and Institution: Audiology, University of Western Ontario

Sponsor: Ontario Research Fund

Ethics Approval Date: February 17, 2011 **Expiry Date:** August 31, 2014

Documents Reviewed and Approved: UWO Protocol. Letter of Information and Consent (Adult/Parent). Assent Letter. Poster x 2, Webpage.

Documents Received for Information:

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced study on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the UWO Updated Approval Request Form.

During the course of the research, no deviations from, or changes to, the protocol or consent form may be initiated without prior written approval from the HSREB except when necessary to eliminate immediate hazards to the subject or when the change(s) involve only logistical or administrative aspects of the study (e.g. change of monitor, telephone number). Expedited review of minor change(s) in ongoing studies will be considered. Subjects must receive a copy of the signed information/consent documentation.

Investigators must promptly also report to the HSREB:

a) changes increasing the risk to the participant(s) and/or affecting significantly the conduct of the study;
b) all adverse and unexpected experiences or events that are both serious and unexpected;
c) new information that may adversely affect the safety of the subjects or the conduct of the study.

If these changes/adverse events require a change to the information/consent documentation, and/or recruitment advertisement, the newly revised information/consent documentation, and/or advertisement, must be submitted to this office for approval.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

[redacted]

Chair of HSREB: Dr. Joseph Gilbert
FDA Ref. #: IRB 00000940

Ethics Officer to Contact for Further Information

[redacted]

This is an official document. Please retain the original in your files.

cc: ORE File
LHRI

UWO HSREB Ethics Approval - Initial
V.2008-07-01 (rptApprovalNoticeHSREB_Initial)

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Page 1 of 1

Appendix B: Results of Within-Epoch Analysis

	Time windows (ms)					
Elicitor		**5-7.5**	**7.5-10**	**10-12.5**	**12.5-15**	**15-17.5**
Ipsi	**7.5-10**	-2.0±5.76; p=1				
	10-12.5	-0.62±5.89; p=1	1.38±2.87; p=1			
	12.5-15	-8.64±6.29; p=0.002*	-6.36±7.33; p=0.107	-8.02±5.23; p=0.000*		
	15-17.5	-9.98±9.86; p=0.045*	-7.98±9.11; p=0.137	-9.36±8.42; p=0.020*	-1.34±9.88; p=1	
	17.5-20	-6.24±9.09; p=0.555	-4.24±8.1; p=1	-5.62±8.03; p=0.505	2.40±7.86; p=1	3.74±10.69; p=1
Contra	**7.5-10**	-1.61±3.88; p=1				
	10-12.5	-1.0±4.21; p=1	-0.60±4.25; p=1			
	12.5-15	-4.62±5.8; p=0.250	-3.01±5.67; p=1	-3.62±4.95; p=0.405		
	15-17.5	-7.54±6.22; p=0.008*	-5.93±6.96; p=0.164	-6.53±6.14; p=0.029*	-2.91±5.82; p=1	
	17.5-20	-8.12±6.51; p=0.006*	-6.51±6.51; p=0.050	-7.11±7.11; p=0.050	-3.49±7.55; p=1	-0.58±8.05; p=1
Binaural	**7.5-10**	-6.96±7.39; p=0.081				
	10-12.5	-8.33±5.97; p=0.002*	1.38±8.59; p=0.002			
	12.5-15	-18.25±5.92; p=0.000*	-11.29±7.54; p=0.001*	-9.92±7.55; p=0.003*		
	15-17.5	-18.24±6.35; p=0.000*	-11.29±7.65; p=0.001*	-9.91±7.44; p=0.003*	.01±6.74; p=1	
	17.5-20	-17.01±6.51; p=0.000*	-10.06±10.18; p=0.055	-8.68±9.65; p=0.113	1.24±7.524; p=1	1.23±7.05; p=1

Mean difference ± 95% confidence intervals of within-epoch temporal analysis from Chapter 6 are displayed along with their respective FDR corrected p. Time windows along columns are compared with time windows in rows. Significant mean differences after FDR correction are indicated with a superscripted asterisk.

Appendix C: Results of Across-Epoch Analysis

		Epoch-time (ms)		
Elicitor		**7-22**	**31-46**	**55-70**
Ipsi	**31-46**	-1.92±4.21; p=1		
	55-70	2.84±5.04; p=0.738	4.76±3.23; p=0.002*	
	79-94	2.91±5.99; p=1	4.83±4.49; p=0.029*	0.70±3.89; p=1
Contra	**31-46**	3.56±3.27; p=0.027*		
	55-70	7.11±4.45; p=0.001*	3.55±3.61; p=0.056	
	79-94	5.99±5.78; p=0.039*	2.44±5.20; p=1	-1.11±4.90; p=1
Binaural	**31-46**	0.51±5.39; p=1		
	55-70	6.98±5.67; p=0.009*	6.46±4.12; p=0.001*	
	79-94	9.36±6.39; p=0.002*	8.85±6.12; p=0.002*	2.39±5.96; p=1

Mean difference ± 95% confidence intervals of across-epoch temporal analysis from Chapter 6 are displayed in the table above. ΔOAEn obtained from clicks presented sequentially every 24 ms after elicitor cessation are compared. Epoch-time along columns are compared with epoch-times in rows. Significant mean differences after FDR correction are indicated with a superscript asterisk. Note that the comparisons are made after collapsing TD and sAPD groups together, considering no group interactions were found in RM-ANOVA.

Curriculum Vitae

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Selected Presentations:

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