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UNIVERSITY OF CALIFORNIA,
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Objective and Subjective Evaluation of Auditory Temporal Processing
DISSERTATION

submitted in partial satisfaction of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

in Biomedical Engineering

by

Jamal Mohammad Alsamri

Dissertation Committee:
Professor Fan-Gang Zeng, Chair
Professor Frithjof Kruggel
Associate Professor Hamid Djalilian, MD

2016

DEDICATION

أهدي هذه الدعوات والآيات الكريمات

إلى والداي العزيزين: ﴿ رَّبِّ ارْحَمْهُمَا كَمَا رَبَّيَانِي صَغِيرًا ﴾
الإسراء-24

My prayers to my parents: "My Lord, have mercy upon them as they brought me up [when I was] little". (The Qur'an, *Children of Israel* 17.24)

وإلى زوجتي وأولادي: ﴿ رَبَّنَا هَبْ لَنَا مِنْ أَزْوَاجِنَا وَذُرِّيَّاتِنَا قُرَّةَ أَعْيُنٍ وَاجْعَلْنَا لِلْمُتَّقِينَ إِمَامًا﴾
الفرقان-74

My prayers to my wife and children: "Our Lord, grant us from among our wives and offspring comfort to our eyes and make us an example for the righteous". (The Qur'an, *The Criterion*, 25.74)

وإلى إخوتي وأخواتي: ﴿ رَبِّ اغْفِرْ لِي وَلِأَخِي وَأَدْخِلْنَا فِي رَحْمَتِكَ ۖ وَأَنْتَ أَرْحَمُ الرَّاحِمِينَ ﴾
الأعراف-151

My prayers to my brothers and sisters, "My Lord, forgive me and my brother and admit us into Your mercy, for You are the most merciful of the merciful ones." (The Qur'an, *The Heights* 7.151)

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ACKNOWLEDGMENTS

I would like to start my acknowledgments by expressing my sincere gratitude and appreciation to my committee chair, Professor Fan-Gang Zeng. I have known Prof. Zeng for almost five years since I first contacted him as a father of kids with auditory neuropathy (AN). Prof. Zeng is one of the well-known researchers in AN, and his name has been associated with half of the top 10 most cited articles in the AN field. Since becoming student under his supervision, I learned not only how to become a successful researcher but also how to become a scholar with a humble character and great values and principles that everyone admires.

I would like to thank my committee members, Professor Frithjof Kruggel and Professor Hamid Djalilian, for their supervision in perfecting this dissertation.

Chapter 2 of this dissertation is excerpted from "Human Envelope Following Responses to Amplitude Modulation: Effects of Aging and Modulation Depth" by Andrew Dimitrijevic, Jamal Alsamri, Michael Sasha John, David Purcell, Sahara George and Fan-Gang Zeng. This work is currently in press in Ear and Hearing, a journal published by Wolters Kluwer Health, Inc.

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ABSTRACT OF THE DISSERTATION

Objective and Subjective Evaluation of Auditory Temporal Processing

By

Jamal Mohammad Alsamri

Doctor of Philosophy in Biomedical Engineering

University of California, Irvine, 2016

Professor Fan-Gang Zeng, Chair

The sense of hearing depends on many physical and biological processes. Much research is focused on different aspects of hearing loss and ways to improve the lives of those with this disability. Auditory neuropathy (AN) is a relatively newly discovered hearing disorder and has been related to damage in the auditory nerve synapses, both pre- and post-synaptic transmission, and the nerve itself. This damage ranges from demyelination to axonal and cell loss. One of the significant deficits that people with AN suffer is their inability to understand speech in a noisy environment. Understanding speech depends on the listener's ability to extract the temporal envelope of the spoken language. Since AN patients have a significant temporal processing deficit, it is difficult for them to understand speech despite the fact that they can hear it. Gap detection and temporal modulation transfer function (TMTF) have been the most common psychophysical tests that are used to measure the severity of impairment in patients with AN. These two subjective tests have frequently been used to evaluate the temporal acuity of patients with auditory neuropathy. However, these tests rely on subjects' active responses to stimuli, which means that they are not feasible for examining infants and patients with some cognitive disabilities that limit their understanding of the task. Therefore, finding an alternative test that can reliably and objectively measure temporal acuity is crucial.

Recent studies suggest that cortical evoked potentials may be used to assess both the severity and lesion sites of AN. However, these cortical potentials are limited to adults and are not easily implemented in an everyday clinical setting.

The present research proposed a new technique that will allow clinicians to objectively measure the auditory temporal processing acuity for patients with auditory neuropathy. The auditory temporal processing acuity for five different groups has been studied using both the conventional subjective test and a newly proposed objective technique. The five groups included 12 younger normal-hearing subjects (18-28 years), 12 older subjects (41-63 years), 12 elderly subjects (67-82 years), two normal-hearing children (10-14), and seven subjects who have been diagnosed with auditory neuropathy (11-43). Some of the subjects in the older and elderly groups had normal hearing thresholds, and some had hearing loss. The newly developed objective technique used a modulated noise in which its amplitude or frequency rate was varied over time to elicit the envelope following response (EFR). Data from the five groups showed a significant correlation between the modulation detection threshold estimated by the EFR and that by behavioral modulation transfer function (MTF). This significant correlation suggests that the EFR can serve as an objective novel technique to evaluate the severity of auditory neuropathy. Together, the EFR-MTF profiles can be related to known sites of lesions in AN. The EFR profile can be used as a biomarker to objectively diagnose auditory processing disorders and to help make treatment options.

INTRODUCTION

Hearing loss is one of the most common disabilities in the world. It is assumed that 13 % of people over the age of 12 years old have a hearing loss (Lin, Niparko & Ferrucci 2011). According to the Centers for Disease Control and Prevention (CDC), on average, two to three infants out of one thousand are diagnosed with different types of hearing loss during their birth screening test (CDC 2010). These people vary by the type and level of their disability, and the type and location of the auditory dysfunction.

The auditory system in humans is a phenomenal and complex system; it shows how the man was fashioned with great wisdom and precision. The peripheral auditory system consists of three major parts: the outer ear, middle ear, and the inner ear. The outer ear, which consists of the pinna and auditory canal, focuses sound pressure waves into the ear canal. The middle ear, which consists of the tympanic membrane (i.e. the eardrum), ossicles and oval window, amplify and deliver the vibrations to the cochlea. Lastly, the inner ear consists of two major sections: semicircular canals, which keep the body in balance, and the cochlea, which is the main hearing sensory organ in the inner ear.   Sound waves travel throughout two major pathways before they reach their ultimate destination in the brain. The peripheral auditory pathway starts from the tympanic membrane and ends at the eighth cranial nerve (vestibulocochlear nerve), whereas the central auditory pathway starts from the cochlear nuclei and terminates in the auditory cortex. There are two main types of peripheral hearing loss: conductive hearing loss and sensorineural hearing loss. Conductive hearing loss usually occurs as a result of an abnormality in the outer or middle ear. Sensorineural hearing loss occurs as a result of damage to the inner ear, which includes the cochlea and auditory nerve.

CHAPTER 1

Auditory Neuropathy

Sensorineural hearing loss refers to any peripheral hearing loss that is a result of a problem in the inner ear or neural pathways. To narrow the sensorineural hearing loss category further, a relatively new and distinct peripheral hearing disorder, auditory neuropathy, was identified by Arnold Starr in 1996. Auditory Neuropathy is clinically defined as an abnormal condition in which patients have intact outer hair cells, as confirmed by normal otoacoustic emissions or cochlear microphonics, but have abnormal signal transmission from the inner hair cells to auditory nerve fibers. This abnormality can be confirmed by missing or deformed auditory brainstem responses (ABR) (Starr et al. 1996). 'Neuropathy' is a medical and neurological term which refers to damage or a dysfunction of the peripheral nerve. Although AN patients have an abnormal or absent ABR, some neural signals reach the auditory cortex to allow the long latency cortical evoked potential to be recorded (Kraus et al. 2000, Michalewski et al. 2005, Narne, Vanaja 2008, Michalewski et al. 2009). Since 'Auditory Neuropathy' is a very general term for the medical condition, researchers and neurologists have started to further specify this disease using functional terms, such as the auditory dys-synchrony spectrum disorder (Starr, Sininger & Pratt 2000, Berlin et al. 2003). "Auditory neuropathy spectrum disorder" is another general term that is also commonly used to classify any condition with these audiological results and symptoms but unknown etiology.

Auditory neuropathy can arise from a presynaptic or a post-synaptic lesion. These lesions' sites can be revealed by some genetic tests (Manchaiah et al. 2011). The pre-synaptic lesion can be defined as an abnormal transmission mechanism that takes place at the synapse of the inner hair cells (IHC) and the eighth cranial nerve. For example, the neurotransmitters that are typically released

from the inner hair cells to activate action potentials in the auditory nerve can be interrupted by mutations in the otoferlin (OTOF) gene (Varga et al. 2006, Rodriguez-Ballesteros et al. 2008). The post-synaptic lesion can be defined as a problem in the auditory nerve itself, and might be associated with additional peripheral neuropathies. For example, the Freidreich's ataxia is considered as another type of AN (Rance et al. 2008). Some patients with space-occupying lesions, such as vestibulocochlear nerve tumors, acoustic neuroma, or with multiple sclerosis, have similar symptoms but are not considered to have auditory neuropathy because their deficits can be explained with abnormalities visible with radiological imaging (Hood 1999).

Auditory neuropathy can also include a recently-discovered form of neuropathy that can result from acoustic overexposure, termed hidden hearing loss (Kujawa, Liberman 2009). A hallmark of hidden hearing loss is a relatively normal audiogram but abnormal suprathreshold function due to neural degeneration. Recent studies suggest that noise-induced and age-related hearing losses have been correlated, and people who have been overexposed to noise, especially as a child, will be more susceptible to age-related hearing loss (Kujawa, Liberman 2006, Sergeyenko et al. 2013). One of the significant deficits that people suffer when they become older is their inability to understand the speech in a noisy environment. Older individuals also show reduced temporal processing ability, which is thought to contribute to deficits in speech perception, especially in a noisy environment (Anderson et al. 2012). In this way, deficits related to aging and noise exposure are similar in nature to deficits resulting from a diagnosis of classic auditory neuropathy.

Envelope Following Response (EFR)

Recently, auditory evoked potentials (AEPs) have been extensively studied for possible use as an objective diagnostic method for evaluating temporal processing acuity. This technique makes it possible to assess infants and individuals with cognitive disabilities who cannot provide reliable feedback in behavioral tests. AEPs can be characterized either by their latency (when they occur relative to a stimulus) or by whether the responses are transient or sustained. Envelope Following Response (EFR) is a specific term for a pattern of auditory evoked potentials that are in between transient and sustained responses and are elicited by changes in stimulus envelope over time (Picton 2010). In some clinical practices, audiologists use a well established objective test that is called the auditory steady-state response (ASSR) to assess hearing thresholds in infants as an alternative to the ABR. ASSR is a type of EFR that is characterized by the periodicity of its stimuli (Picton 2013). The auditory steady-state response (ASSR) is typically elicited by amplitude-modulated, frequency-modulated or both amplitude- and frequency-modulated stimuli. The neural response arises at the modulation rate and is evaluated in the frequency domain. One advantage of using the ASSR technique is that it does not need the experimenter to make any subjective judgment on the presence or absence of an evoked response waveform. Alternatively, ASSR uses objective statistical methods in the discrimination of the auditory response (Picton et al. 2003). Furthermore, ASSR can evaluate thresholds of both ears simultaneously in shorter testing time if multiple carrier frequencies tested in each ear is modulated at a unique rate (John et al. 1998).

One efficient EFR technique introduced by Purcell and colleagues (2004) uses a sweeping modulation, in which the modulation rate is continuously and systematically increased or decreased over time. Figure 1.1 shows the waveform of a sample sweeping modulation stimulus and Figure 1.2

represents the EFR to such a stimulus. There are several advantages of using the sweep technique over other conventional approaches (e.g. sequential measurement at fixed modulation rates). First, the sweep technique provides a higher resolution compared to discrete stimuli. Also, with the sweep technique, artifacts as a result of unintended movement will affect all modulation rates equally and be easier to find and eliminate. Finally, the sweep technique improves control of the adaptation effect and the subject's arousal state (Purcell et al. 2004); these factors will affect all modulation rates equally for a better comparison.

Purcell et al. (2004) showed that the EFR in normal hearing subjects was generally significant for modulation rates up to 500 Hz with an insignificant response near 70 Hz at which the response transits from a cortical origin (<71 Hz) to a brainstem origin (Plourde, Stapells & Picton 1991, Herdman et al. 2002). Purcell et al. (2004) also found a significant correlation between the subjective tests such as modulation and gap detection and the EFR results. Since auditory neuropathy will likely affect both subjective and objectively temporal processing measures, a stronger correlation in individuals with AN than in the normal hearing subjects can be predicted.

Figure 1. 1: Envelope Following Response: the amplitude for the range 20 to 100 Hz from a single individual in response to 25% amplitude modulated white noise presented at 60 dB SPL modulated from 20 to 100 Hz. In a normal hearing subject (thick line= awake EFR & thin line=sleeping EFR). Taken from Purcell et al. (2004).

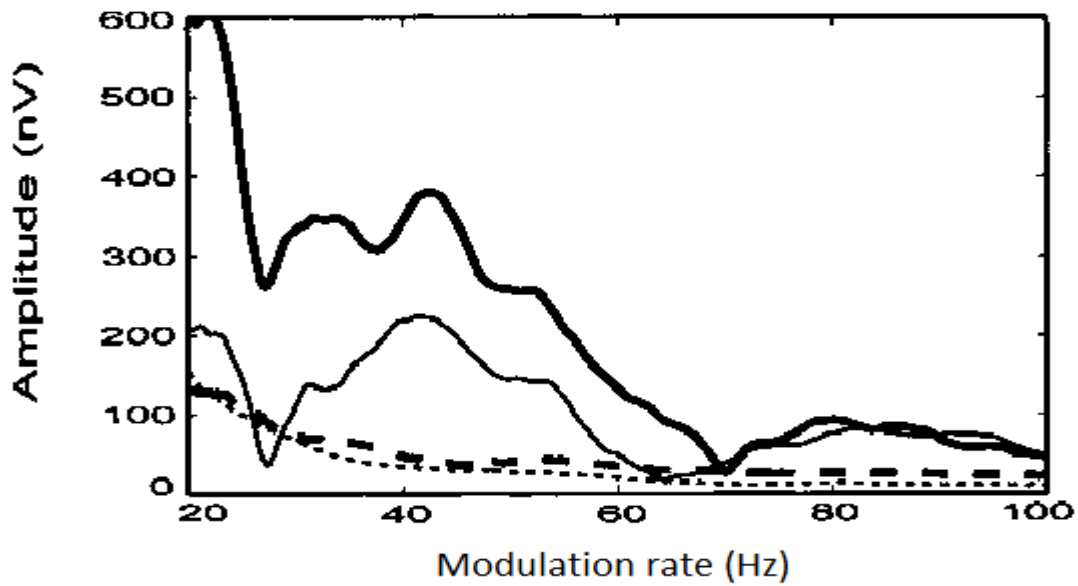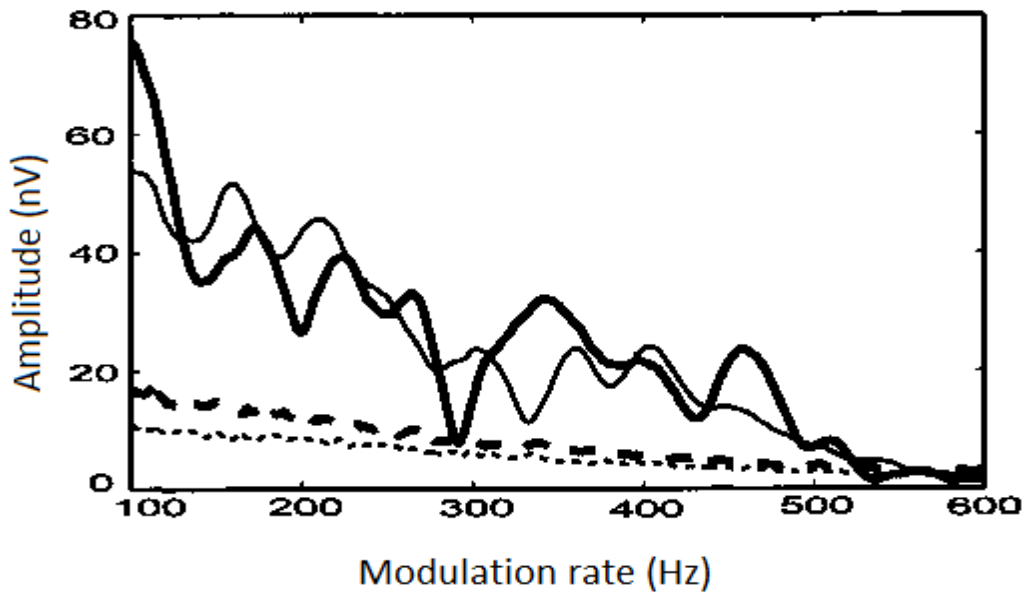**Figure 1. 2: Envelope Following Response: the amplitude for the range 20 to 100 Hz from a single individual in response to 25% amplitude modulated white noise presented at 60 dB SPL modulated from 100 to 600 Hz. In a normal hearing subject (thick line= awake EFR & thin line=sleeping EFR), the EFR was significantly different from noise floor (the dashed line) up to a modulation rate of 500 Hz. Taken from Purcell et al. (2004).**

CHAPTER 2

Human Envelope Following Responses to Amplitude Modulation: Effects of Aging and Modulation Depth

ABSTRACT

OBJECTIVE: To record Envelope Following Responses (EFRs) to monaural amplitude-modulated broadband noise carriers in which amplitude modulation (AM) depth was slowly changed over time and to compare these objective electrophysiological measures to subjective behavioral thresholds in young normal hearing and older subjects.

DESIGN: Participants: three groups of subjects included a young normal hearing group ("YNH", 18 to 28 years; pure tone average=9 dB HL), a first older group ("O1"; 41 to 62 years; pure tone average=30 dB HL) and a second older group ("O2"; 67 to 82 years; pure tone average=49 dB HL). Electrophysiology: In condition 1, the AM depth (41 Hz) of a white noise carrier, presented at a suprathreshold intensity of 60 dB SL, was continuously varied from 2% to 100% (5%/sec). EFRs were analyzed as a function of the AM depth. In condition 2, auditory steady-state responses (ASSRs) were recorded to fixed AM depths (100, 75, 50, and 25%) also presented at 60 dB SL with an AM rate of 41 Hz. Psychophysics: A three alternative, forced-choice procedure was used to track the amplitude modulation (AM) depth needed to detect AM at 41 Hz (AM detection). The minimum AM depth capable of eliciting a statistically detectable EFR was defined as the physiological AM detection threshold.

RESULTS: Across all ages, the fixed AM depth ASSR and swept AM EFR yielded similar response amplitudes. Statistically significant correlations (r=0.48) were observed between behavioral and

physiological AM detection thresholds. Older subjects had slightly higher, but non-significant behavioral AM detection thresholds than younger subjects. AM detection thresholds did not correlate with age. All groups showed a sigmoidal EFR amplitude vs. AM depth function but the shape of the function differed across groups. The O2 group reached EFR amplitude plateau levels at lower modulation depths than the NH group and had a narrower neural dynamic range. In the YNH group, the EFR phase did not differ with AM depth whereas in the older group, EFR phase showed a consistent decrease with increasing AM depth. The degree of phase change (or phase-slope) was significantly correlated to the pure tone threshold at 4 kHz.

CONCLUSIONS: EFRs can be recorded using either the swept modulation depth or the discrete AM depth techniques. Sweep recordings may provide additional valuable information at suprathreshold intensities including the plateau level, slope and dynamic range. Older subjects had a reduced neural dynamic range compared to younger subjects suggesting that aging affects the ability of the auditory system to encode subtle differences in the depth of amplitude modulation. The phase-slope differences are likely related to differences in low and high-frequency contributions to EFR. The behavioral-physiological AM depth threshold relationship was significantly but likely too weak to be clinically useful in the present individual subjects who did not suffer from apparent temporal processing deficits.

INTRODUCTION

Temporal processing of sound is a crucial aspect in many areas of audition including sound detection, localization, and identification. Much of the information required to understand spoken language comes from the temporal envelope of speech as evidenced by our ability to understand speech with limited spectral cues (Fu 2002, Shannon et al. 1995). Insights into the importance of temporal processing for speech are also seen with disorders arising from auditory temporal processing difficulties, such as auditory neuropathy (Starr et al. 1996) resulting in impaired speech perception (Zeng, Liu 2006). In older individuals, reduced temporal processing ability is thought to contribute to deficits in speech perception especially in noise (Anderson et al. 2012). The reduction in temporal processing in the elderly is in part associated with reductions in inhibitory neurotransmitter at various levels of the ascending auditory system including the brainstem (Wang et al. 2009), thalamus (Richardson et al. 2013) and auditory cortex (Caspary, Hughes & Ling 2013). This altered balance of inhibition may also be related to a reduction in neural synchrony that is normally required for precise speech encoding. Modeling auditory aging as temporal disruptions through neural jitter provides evidence that reduced temporal processing, as opposed to reduced spectral processing, is more related to reductions in speech perception in the elderly (Pichora-Fuller et al. 2007).

One commonly used method of assessing temporal processing is the temporal modulation transfer function (TMTF). The TMTF is obtained by determining the behavioral threshold for minimum modulation needed to detect amplitude modulation (AM) as a function of modulation rate. The TMTF typically has a low-pass filter shape such that AM detection threshold changes little across low frequencies (~2 to ~50 Hz). Beyond that range the AM detection threshold increases significantly, resulting in a low-pass filter characteristic (Viemeister 1979). Behavioral

measures of TMTFs in the elderly have shown overall similar shapes to young normal-hearing listeners. Elderly listeners (above 70 years) showed slightly elevated AM detection thresholds, especially for AM rates above 30 Hz (Takahashi, Bacon 1992). Therefore, we hypothesized that in this study, a relatively small, but detectable, difference in behavioral TMTFs would be observed between young and elderly listeners.

The use of auditory evoked potentials to examine temporal processing has been the topic of a recent review by Picton (2013). In that review, it was noted that temporal resolution is often assessed using AM stimuli to evoke brain responses, by gap detection, or by recognition of single versus double stimuli. In this report, we will focus on the brain's response to AM stimuli, which are often referred to as Auditory Steady-State Responses (ASSRs). By definition, ASSRs have a stable amplitude and phase across time because the evoking stimulus (e.g., AM) is constant. However, in cases where the evoking stimulus changes over time, as is the case for speech stimuli (Aiken, Picton 2008) or changing AM (Purcell et al. 2004), the brain response also changes. These responses are often termed Envelope Following Responses (EFRs). In effect, an ASSR is a subclass of EFRs. We recorded both ASSRs (to fixed AM depths) and EFRs (to changing AM depth), but these terms may be used here interchangeably, in accordance with the terms used by prior studies.

A number of ASSR and EFR studies have examined the temporal processing ability of the auditory system in young normal hearing and elderly participants. Purcell et al., (2004) described an EFR method of assessing temporal processing by presenting an AM stimulus that varied in modulation rate as a function of time. The brainstem EFR (modulation rates above 70 Hz AM) was significantly correlated to behavioral measures of gap and AM detection. Ross et al. (2000) examined ASSRs to a wide variety of AM rates (10 to 98 Hz) and found that the shape of the

ASSR amplitude versus AM rate function resembled a psychophysically-derived TMTF. In a study that examined ASSRs and aging, Boettcher et al., (2001) recorded ASSRs to stimuli with high and low frequency pure tone carriers at an AM rate of 40 Hz with various AM depths. In the elderly with high frequency hearing loss, ASSRs to a low frequency carrier were reduced compared to normal hearing (NH) controls. Further, this was not found in older subjects with no high frequency hearing loss. Along similar lines, Leigh-Paffenroth & Fowler (2006) examined high and low frequency carrier ASSRs at different AM rates (20, 40, 90 Hz) and found that older subjects had reduced ASSR phase-locking at all AM rates and that ASSRs to a low frequency carrier were correlated with speech perception measures. In their study, some of the elderly subjects had some degree of high frequency pure tone behavioral threshold elevation. Both of these studies suggest that in typical aging, a reduction in the ASSR (amplitude/phase locking) is observed primarily with low frequency carriers.

The current study differs from these prior studies of aging and ASSRs in a number of ways. A white noise carrier was chosen instead of a tonal carrier because noise carriers elicit more robust ASSRs that decrease testing time, likely due to the noise activating the entire cochlea (John, Dimitrijevic & Picton 2003). We also opted for a white noise carrier because such stimuli are often used in psychoacoustic studies of temporal processing and therefore allow comparisons across different studies. A second difference was the exploration of AM depth as an independent variable rather than using AM rate or other characteristics. A third difference was the use of a continually swept stimulus as opposed to presenting at discrete AM depths. An advantage of such a technique is that finer resolution of neural activity is possible above and below threshold.

Conceivably, the "neural AM depth threshold" could be estimated by determining the AM depth at which the response transitions from being significant (suprathreshold AM depth) to non-

significant (subthreshold AM depth). The rationale for this approach is similar to previously reported "sweep" or "zoom" techniques (Linden et al. 1985, Rodriguez et al. 1986, Poulsen, Picton & Paus 2007) for intensity threshold estimations. Another reason for choosing a swept AM depth over discrete AM is that this approach allows for a more accurate characterization of the EFR growth function with increases in AM depth. Large steps in discrete AM depths may easily miss subtle differences in function shapes (e.g., linearly increasing versus sigmoidal shapes).

The current study measured physiological AM processing in the auditory system because it could provide an objective measure of behavioral temporal processing ability. We also chose to include elderly adults because deficits in temporal processing with normal aging have been well established (Gordon-Salant, Fitzgibbons 1999). Further, we assessed the ability of physiological data to estimate behavioral thresholds for AM detection since this may be clinically relevant in detecting functional decrements in processing capacity. In summary, the goals of this study were: (1) determine if the swept AM depth approach corresponds to fixed AM depths and is a viable technique to elicit EFRs; (2) relate the EFR AM depth threshold to behavioral AM depth thresholds; (3) examine differences in AM depth thresholds in young NH and older listeners using both the EFR and behavioral responses; (4) compare AM depth-EFR growth functions in young NH and older listeners.

MATERIALS AND METHODS

Subjects

A total of 38 adults (15 females) participated in the study, comprising a YNH group (n=12, aged 18 to 28 years, mean 23 years, 7 females), a first older group (O1; n=12, aged 41 to 63 years, mean 55 years, 4 females) and a second older group with a higher mean age (O2; n=12, aged 67

to 82 years, mean 74 years, 4 females). All YNH individuals had normal pure tone thresholds (less than 20 dB HL) measured at 250, 500, 1000, 2000, and 4000 Hz. This was assessed using ER3A earphones and a GSI 61 Clinical audiometer with a 10 dB down/5 dB up bracketing procedure. Subjects in the O1 and O2 groups had elevated pure tone audiograms, consistent with age-related hearing loss.

The experimental protocols were approved by the Institutional Review Board of the University of California Irvine. Subjects were recruited from the Center for Hearing Research at Irvine database and the University of California Irvine student community. Written informed consent was obtained from each subject after the nature of the study was explained. Subjects were paid to participate in the study.

Stimuli

For all evoked potential stimuli, a wideband noise carrier (using the Matlab function rand.m) was amplitude modulated at the fixed rate of 41.0156 Hz. Evoked responses to fixed AM depths were obtained using depths of 100%, 75%, 50% and 25% and consisted of 16 epochs of 1.024-sec each and each recording trial included 30 such sweeps. A swept AM stimulus used modulation depths ranging from 2% to 100% across each stimulus sweep of 40 epochs. Each swept stimulus condition was comprised of three replication trials of 30 sweeps each, and each replication lasted 20.48-mins for a total recording time for swept data of approximately 1 hour. The AM% depth was ramped linearly upward during the first 20.48 seconds of the sweep (20 epochs) and linearly downward over the same range during the second 20 epochs. The rate of change of amplitude modulation depth was 4.785% per second. Sweeps were constructed so that they could be concatenated and repeated without acoustic transients (Purcell et al. 2004). Fixed

depth stimuli were recorded for 11 minutes at each depth for depth at 100%, 75%, 50%, and 25% for a total of 44 minutes.
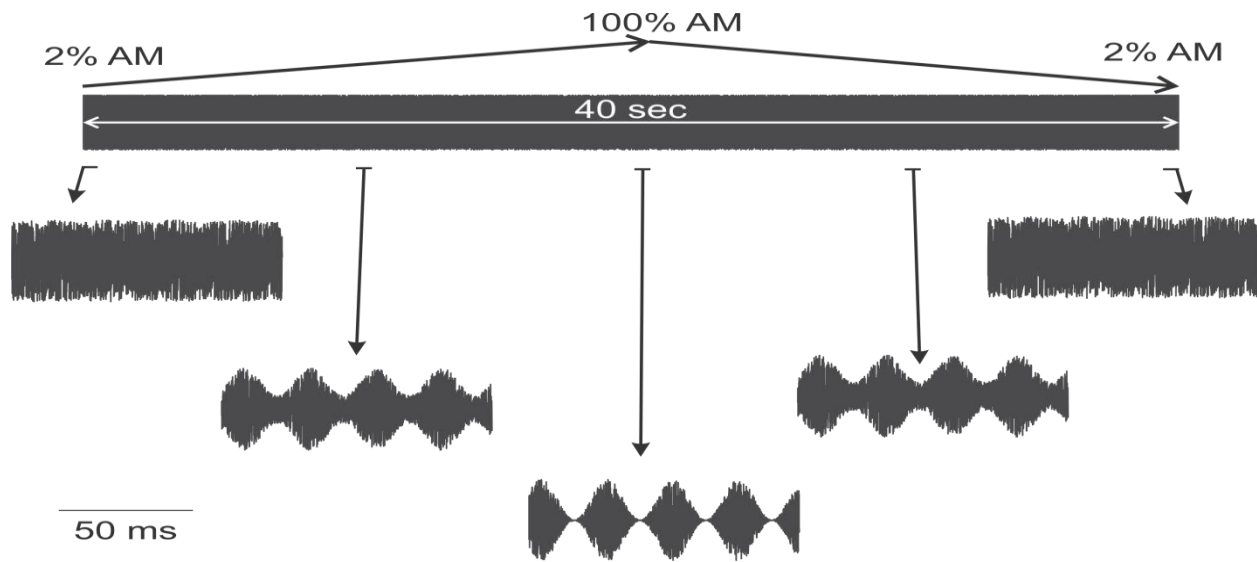
Figure 2. 1: A 40-second segment of the swept AM depth stimulus is shown. The modulation rate was held constant at 41 Hz, while the AM depth varied from 2 to 100% for the first 20 seconds and then 100% to 2% for the last 40 seconds. No transient sounds were heard across successive repetitions of the 40-second sound. Samples of 50 msec are shown to illustrate the AM depth at different time points. AM indicates amplitude modulation.

Both fixed and swept EFR stimuli and stimuli for the psychoacoustic AM detection (see below) were presented to the right ear. In some cases where the pure tone threshold was elevated more in the right ear, the left was used. The right ear was used for all 12 of the YNH subjects, 10 out of 12 subjects for the O1 group, and 11 out of 12 subjects for the O2 group. Stimuli were presented at 68 dB SPL for the YNH group and at loud but comfortable levels for the O1 and O2 groups (Table 1). The sound pressure level of the 0% AM stimulus was measured using a Brüel and Kjær sound level meter (Investigator 2260) in a 2cc coupler DB0138 set on A weighting with a "slow" time constant. A wideband noise carrier has energy at all frequencies, but when presented through the Etymotic ER3A transducer, energy above 5 kHz is attenuated by more than 10 dB, reaching 30 dB attenuation by 7 kHz.

14

All 36 subjects were tested in the sweep AM condition, however due to time constraints for some of the subjects, only 24 subjects participated in the fixed AM depth condition (YNH, n=9; O1, n=5; O2, n=10).

Stimulus Presentation and Physiological Response Recording

The experiment was controlled by software developed using LabVIEW (Version 8.5, National Instruments). A National Instruments USB-6221 BNC X-series acquisition system provided digital-to-analog conversion of the stimulus with 16-bit resolution at a rate of 32,000 samples/sec. The level of the stimuli were adjusted by routing the signals through an GSI-61 Clinical audiometer. The sounds were produced using an Etymotic ER3A earphone whose sound tube was sealed in the ear-canal using a disposable foam insert. The EEG was recorded from three gold plated Grass electrodes using GRASS Technologies EC2 electrode cream. Electrodes were located at the vertex (Cz; noninverting) and just below the hairline at the posterior midline of the neck (inverting) with a ground (or common) on the collarbone.

Electrode impedances were assessed using an F-EZM5 GRASS impedance meter and were <5000 ohm at 10 Hz. Inter-electrode differences were <2000 ohm. The three electrode leads were braided and then connected to a GRASS LP511 amplifier that applied a gain of 50,000, and a filter having a pass-band of 0.3 to 300 Hz. The 6221 system applied a further gain of two (for a total gain of 100k) before digitizing the output signal of the GRASS amplifier at 32,000 samples/sec using 16-bit resolution.

Data were collected with subjects residing in a sound-insulated and electromagnetically shielded booth. Subjects reclined in a comfortable chair with a pillow under their neck to help support their head. The lights were on, and they were allowed to watch a muted, closed-captioned

movie of their choice. A window was available in order to view the subject to confirm that the subject remained awake. In between recordings, the subject was encouraged to take breaks. The full recording session lasted between 2.5 and 3 hours, including condition 1 (swept AM depth), condition 2 (fixed AM depth), behavioral testing of AM detection, set-up, hearing testing, and breaks.

Physiological Response Analysis

Real-time summary results and indices of EEG signal quality were displayed during data collection to monitor the quality of the recordings and inform if a subject was producing too much EMG activity. A more extensive sweep analysis was then performed off-line using a custom LabVIEW 8.5 program derived with improvements from previous studies (Purcell et al. 2004, Purcell et al. 2006). In the offline analysis, individual 1.024-sec epochs were automatically rejected by the software from a synchronous average sweep if they did not meet certain criteria. First, a noise metric was calculated for every epoch of a stimulus condition by determining the average amplitude of EEG frequencies in a 20 Hz band spanning the modulation rate of the evoking stimulus (31 to 51 Hz). The mean and standard deviation (SD) of this noise metric was calculated across all epochs. A rejection criterion was then set using the mean +2SD, and all epochs that exceeded this criterion were rejected from the mean response sweep. Additionally, epochs were automatically rejected by the software if any saturation of the amplifier occurred (for example, due to a large myogenic artifact from subject movement) as reflected by points of the recorded EEG waveform having either the maximum or minimum value of the analog to digital converter. This rejection procedure can lead to a different number of epochs contributing to each of the 40 mean epochs that comprise an averaged sweep. If many epochs were rejected, then this might be a cause for concern due to different signal-to-noise ratios (SNRs) for different portions of the averaged

sweep. In practice, only 2.5% of epochs were typically rejected, and these were randomly distributed across the averaged sweep. Non-rejected data were synchronously averaged in the time domain to create a mean response sweep (John, Dimitrijevic & Picton 2001).

The ASSRs were measured in the mean sweep data using a software implemented Fourier analyzer (FA), (Regan 1989, Purcell et al. 2004, Purcell et al. 2006). In this method, orthogonal reference sinusoids are matched in frequency to the instantaneous stimulus modulation rate of 41.0156 Hz. An estimated physiological delay of 30 ms was used to improve alignment between the reference and response waveforms during the analysis (Aiken, Picton 2006). This single delay is an estimate of the physiological delays present in a 40 Hz ASSR composed of both cortical and brainstem sources (Purcell et al. 2004; see their Table I "30-50 Hz apparent latency" column where younger and older groups had delays of approximately 25 and 35 ms, respectively). The slow sweeping of AM% depth used here (i.e., 4.785% per sec), likely caused this delay correction to have a very small effect on the estimated response, but it is prudent nonetheless. Two 1.024 seconds rectangular window filters were applied in series to each of the complex outputs of the FA. Because the mean response sweep was evoked by a stimulus with symmetrical increasing and decreasing modulation depths in each half, the second half of the FA output was folded over and vector averaged with the first half. This was done to improve the SNR of the measured responses. A final 512 ms smoothing filter was applied to the amplitude values calculated from the complex FA outputs. To provide a cross-check for the FA results, a discrete Fourier transform (DFT) was also used to estimate the ASSR in the fixed AM% depth condition after similar noise rejection and sweep averaging.

The probability that the estimated ASSR amplitude was drawn from the distribution of the background noise was determined using an F-ratio (Zurek 1992). The characteristics of the

background noise were estimated using a DFT calculated from the mean response sweep folded and averaged in the time domain. For the fixed depth conditions, the average noise levels in +/- 60 DFT frequency bins (having 0.122 Hz frequency resolution for a total range of +/-7.32 Hz) were multiplied by a scaling factor of 2.43 (determined using simulated noise) to compensate for the narrower effective bandwidth of the DFT compared with that of the FA. For the swept depth condition, the average noise levels in +/- 143 DFT bins (having 0.049 Hz frequency resolution for a total range of +/-6.98 Hz) were multiplied by a scaling factor of 3.72. Only the noise estimates were multiplied by these scaling factors, so they could be compared directly with the ASSR amplitudes determined by the FA. The ASSRs were considered significantly different from the background noise estimates when the SNR was ~5 dB. In other words, to reach a $p<0.05$ level, the amplitude F-ratio evaluated using 2 and 240 degrees of freedom for fixed depth conditions must be above 1.742. For the swept depth condition, there were 2 and 572 degrees of freedom, with a critical value of 1.735 (John, Picton 2000).

Physiological Threshold Estimation.

The physiological threshold for detection of amplitude modulation was defined as the smallest modulation depth for which the corresponding ASSR amplitude led to a detectable ASSR with an F-ratio probability value of less than 0.05.

Behavioral Threshold Testing.

Behavioral Modulation thresholds were measured using a three-alternative forced choice (3AFC) tracking procedure carried out using a custom built MATLAB testing program. Based upon the subject's preference, one ear was selected to receive the stimuli to during the 3AFC test.

During each trial of the 3AFC procedure, three sounds are presented sequentially. The sounds were randomly selected to be a wideband noise which was sinusoidally modulated at 41 Hz or two different wideband noises. The observer was required to identify the sound that contained the modulated noise and was provided with feedback from the program which indicated whether the choice was correct. Reversals occurred when a subject incorrectly/correctly responded to two or more consecutive stimuli or vice versa. A large step size (50% change in modulation depth) was used for the first three reversals and then a smaller step size (20% change in modulation depth) was used for the remaining reversals (i.e., an adaptive step size was relied upon). Each run had a total of 12 reversals and the threshold was calculated as the mean of the last eight reversals.

Statistical Analysis

The data were analyzed using repeated measures ANOVA and Pearson correlations. Specific details are described when referred to in the results.

In order to quantify the differences in shape of the EFR as a function of AM depth we modeled individual EFR amplitude versus AM depth results in a customized Matlab sigmoidal function fit using the following formula:

$$EFR\ magnitude = Noise + \frac{A}{(1 + e^{\frac{-(AM\ depth - x50)}{B}})}$$

The following parameters were fit for each EFR versus AM depth recording:

Noise and A were the upper and lower limits of the function. B determined the degree of linearity of the function such that with small values of B, the EFR amplitude remains at low amplitude for much of the AM depth range, followed by a sharp increase in amplitude (steep slope) and finally

a plateau. With large values of B, the shape of the function resembles a linear function with a shallow slope. The X50 component reflects the AM depth for which the EFR amplitude is 50% of its maximum value. For a sigmoid function, this will cause shifts left and right. Two further measures were derived from the model: the knee point of the AM depth at which the function begins to saturate, and the dynamic range (DR). The DR is the AM % difference between 10% and 90% of the EFR amplitude range. Therefore, if a function was sigmoidal with a steep slope, the AM difference between 10% and 90% of EFR amplitude (DR) would be very small. A shallow function on the other hand would have a large DR.

In addition to the EFR magnitude, the EFR phase was also examined as a function of AM depth. In contrast to the magnitude, phase showed a general decrease with increasing AM depth. The phase vs. AM depth relationship was quantified using a linear regression model in the form of $y=mx+b$ where m equals the slope, y equals the phase, and x equals the AM depth, and b the intercept where the phase at 0 AM depth. Because the phase of EEG noise can vary anywhere from 0 to 360º, only significant EFRs were submitted to the linear regression, and this included AM depths that ranged from 25% to 100%. Mean slopes and intercepts were calculated for each subject in the three different groups.

RESULTS

Two of the 38 participants were removed from data analysis. One NH subject requested to be removed from the study before he completed the full testing session and one O2 subject was excluded because of excessive noise due to muscle artifact. In a clinical situation, these subjects would have been re-tested or would have required that the testing session duration be increased (to allow sufficient time to improve SNR through extended averaging). This was not performed in the current study because of time constraints of our subjects.

Behavioral data:

An ANOVA showed that the behavioral pure-tone thresholds were elevated in the O2 group compared to YNH for 500 Hz [main group effect: $F(2,29)=5.9$; $p=0.007$ and post-hoc YNH vs. O2, $p=0.005$] and for 1000 Hz [main group effect: $F(2,29)=7.0$; $p=0.003$ and posthoc YNH vs. O2, $p=0.002$]. For 2000 Hz, the O2 group had greater thresholds compared to both YNH and O1 groups [main group effect: $(F2,29)=14.0$; $p<0.001$ and posthoc YNH vs. O2, $p=0.001$ and O1 vs. O2, $p=0.012$]. For 4000 Hz, the YNH group, had lower thresholds compared to both O1 and O2, and the O1 and O2 groups did not differ [main group effect: $(F2,29)=17.0$; $p<0.001$ and posthoc YNH vs. O1, $p=0.005$ and YNH vs. O2, $p<0.001$].

Table 2. 1: Summary of the pure-tone audiograms and AM detection thresholds for both behavior and EFR

Group	Age	Pure tone threshold (Hz)				AM threshold (%)		Stimulus Intensity (dB SPL)
		500	1000	2000	4000	Behavioral	EFR	
YNH	22(3)	8(8)	8(5)	5(8)	2(6)	11.7(4)	9.1(3.1)	68
O1	55(7)	17(14)	14(11)	15(15)	29(15)	12.8(3.9)	11.9(4.8)	71(4), 78-67
O2	75(6)	31(19)	33(17)	38(17)	50(28)	14.6(6.5)	11.3(9.8)	81(6), 73-93

SDs are shown in parenthesis. For the last column, stimulus intensity, this was the presentation level for both the AM detection and EFR measures. The last two numbers indicate the range. AM, amplitude modulation; EFR, envelope following response; O1, first older group; O2, second older group; YNH, young normal-hearing group.

Pure tone and AM detection thresholds for all three groups are given in Table 1. Although the mean for AM detection showed that YNH had the lowest AM thresholds, followed by O1, then O2, no significant group differences were observed.

Even though no group differences existed for AM detection, subtle differences may have been obscured by the averaging procedure across set age groups. Therefore we decided to correlate AM detection with age. Figure 2 shows mean AM detection thresholds for modulated broadband noise across the three groups with individual thresholds plotted as a function of age. No significant correlation was found between age and AM detection thresholds, nor was any significant correlation observed between any of the pure tone thresholds and AM detection results. However, as expected, significant correlations were observed between the pure tone thresholds and age [500 Hz, r=0.72; 1000 Hz, r=0.55; 2000 Hz, r=0.65; 4000 Hz, r=0.70; all at p<0.001].
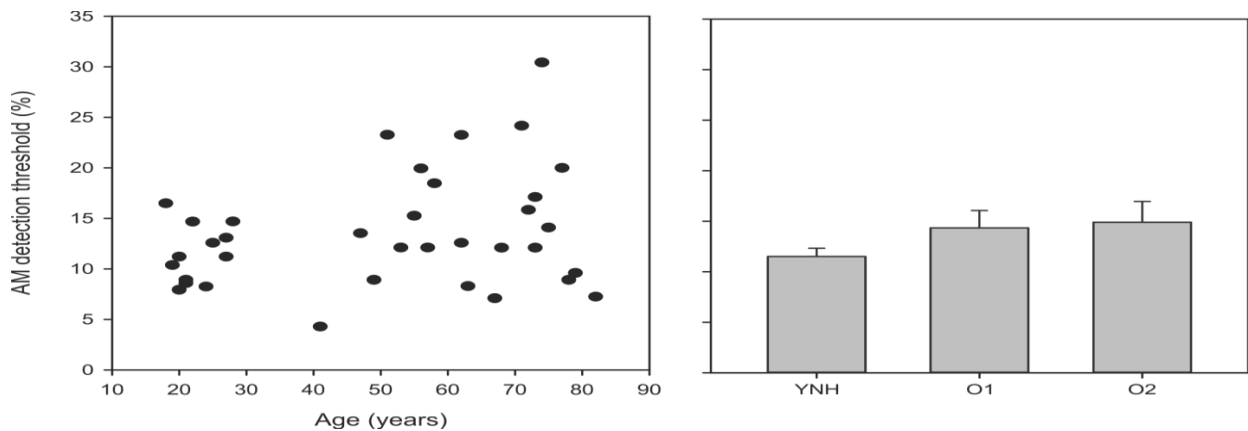

Figure 2. 2: The left panel shows a scatter plot of the age of the subjects with their corresponding behavioral AM detection thresholds. More variability is seen in AM detection threshold with increasing age, but no systematic increase in AM threshold was seen with age. The right panel shows mean AM detection thresholds for the three groups. Error bars are standard error of the mean. AM indicates amplitude modulation.

Electrophysiology:

Sweep EFRs - Amplitude

Significant responses were recorded for all subjects. The general pattern of the EFR amplitude was greater amplitude with larger AM depths. With low AM depths approaching behavioral threshold, the EFR became non-significant. Figure 3 shows a sample subject whose EFR became non-significant at the same AM depth as behavioral threshold. The lowest AM depth for which a significant EFR could be recorded was defined as the EFR threshold (dashed line indicates the noise estimate). In this particular subject, both AM behavioral detection and EFR threshold were 8%. In some instances (10 out of the 39 subjects) there were small regions of non-significant responses (typically spanning a range less than 5% at low AM depths) even though the response was significant again at lower AM depths. These regions of non-significance likely represent instances of an EFR that is near threshold, but may have higher transient noise at these particular times in the recording sweep. Setting the EFR threshold at a higher AM depth, above the regions of non-significance would likely overestimate the threshold EFR depth. We therefore decided to adapt a threshold rule we previously used for estimating ASSR pure tone thresholds (Dimitrijevic et al. 2001) where regions of a response function might show a non-significant value even though there was a significant response at lower intensities. In the current study, if the region of non-significance was less than 5% (17 bins) and the response became significant at a lower AM depth, it needed to remain continuously significant for at least 5% in order to be used in the threshold estimation.
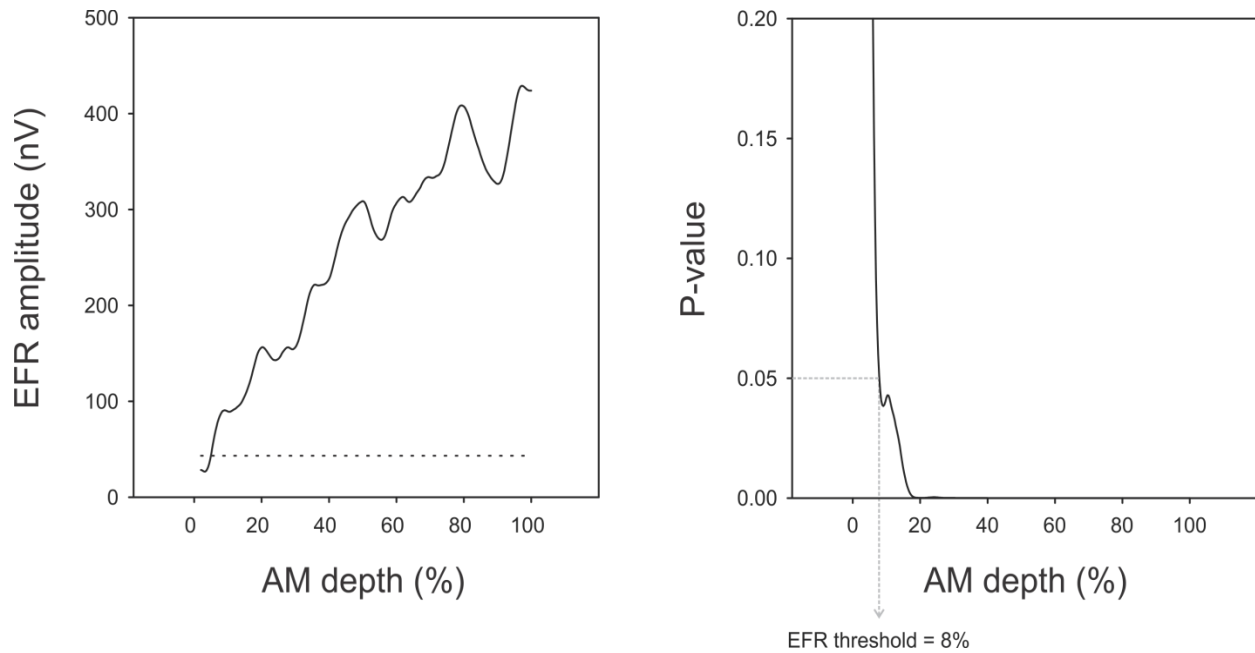
Figure 2. 3: EFR amplitude (left panel) and p-value (right panel) as a function of AM depth is shown for a sample subject. The noise floor of the EEG recording is shown as a horizontal dashed line on the left panel. Determination of EFR threshold was based on the lowest %AM depth where the EFR was significantly different from the background noise (p < 0.05). On the right panel, the dotted line indicates the lowest %AM depth where the EFR was significant (p = 0.05). In this case, the EFR threshold was 8%. In this subject, the behavioral threshold for AM detection was also at 8%. AM indicates amplitude modulation; EEG, electroencephalography; EFR, envelope following response.
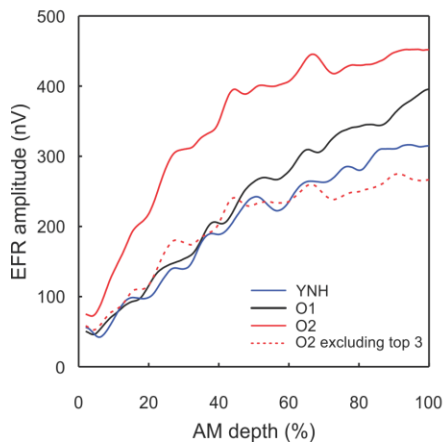
EFRs separately averaged across each of three groups are shown in Figure 4. The YNH subjects appeared to have a relatively linear increase in EFR amplitude while the O2 appeared to have a different shape resembling a sigmoid. Note that there were three O2 subjects who had extremely large EFR amplitudes and mean EFR waveforms were re-plotted excluding these three subjects. The averages of the top five EFR amplitudes (typically elicited by the 95 to 100% AM depth portion of the stimulus) were 400 and 341 nV for YNH and O1, respectively. For O2, the top five amplitude means for all twelve subjects was 491 nV. The three subjects with abnormally large amplitudes, had top five amplitude means of 700, 991 and 1190 nV. Without these three subjects, the mean EFR amplitude was 335 nV, and much closer to the O1 group. It should be noted that we believe these abnormally large EFRs are genuine responses. All three of these subjects were re-tested in a follow up session, and had similar EFR magnitudes to the first session.

We also verified that no artifact was present (that might present as erroneously large responses) in the follow up session with occluded insert earphones. With the occluded earphone approach, there is no sound delivered to the ear and therefore no biological responses should be present. However, we would expect a 5% false positive rate if the EFR/ASSR detection criteria was set to $p<0.05$.

Individual subjects overlaid
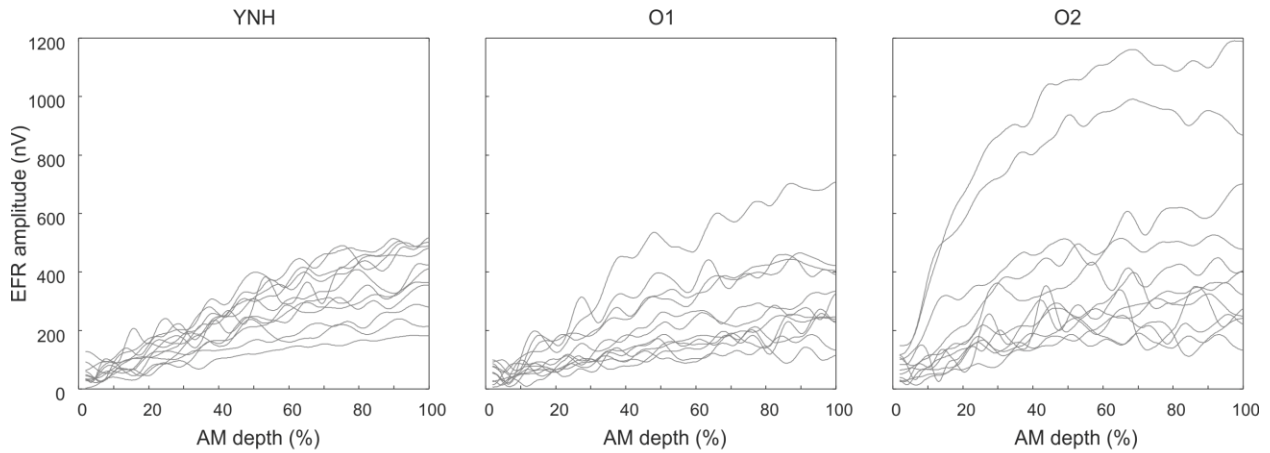
Group mean data

Figure 2. 4: EFR amplitude as a function of %AM depth for all three groups. The top panel shows all subjects overlaid (grey) for the YNH (left), O1 (middle), and O2 group was subdivided into two groups: all subjects n = 12, solid red and excluding the top 3 subjects showing abnormally large EFRs n = 9, dashed red. AM indicates amplitude modulation; EFR, envelope following response; O1, first older group; O2, second older group; YNH, young normal-hearing group.

Averages of the EFR modeled responses across the different groups are shown in Figure 5. The general shape of the EFR amplitude vs. AM depth function resembled a sigmoid. However, the degree of linearity (quantified by the B parameter) appeared to vary among groups, such that YNH and O1 groups appeared more linear and the O2 group appeared to saturate at the maximum EFR amplitude. The mean parameters of the model fits are shown in Figure 6.

	YNH	O1	O2	O2*
A (max)	380	313	430	273
B (linearity)	19	17	12	11
knee point	44	57	48	52
noise floor	15	20	15	19
dynamic range	59	53	40	39
X50 (%AM for 50% max EFR)	41	42	24	25

* excluding the top 3

Figure 2. 5: Modeled EFR data using the same data as Figure 4. The top panel shows all subjects overlaid (gray) for the YNH (left), O1 (middle), and O2 (right) groups. The group's mean data is shown on the bottom left. The bottom right portion of the figure summarizes the parameter values of the model fits across the groups. The A parameter represents the maximum value of the EFR. The B value represents the linearity of the function. With large values, the function is more linear with a shallow slope, whereas with small values, the function resembles a sigmoid with a steep slope on the linear portion. The knee point is the AM depth at which the function begins to saturate. The dynamic range is the AM% difference between 10% and 90% of the EFR amplitude range. The X50 is the %AM where EFR is half the maximum amplitude. AM indicates amplitude modulation; EFR, envelope following response; O1, first older group; O2, second older group; YNH, young normal-hearing group.
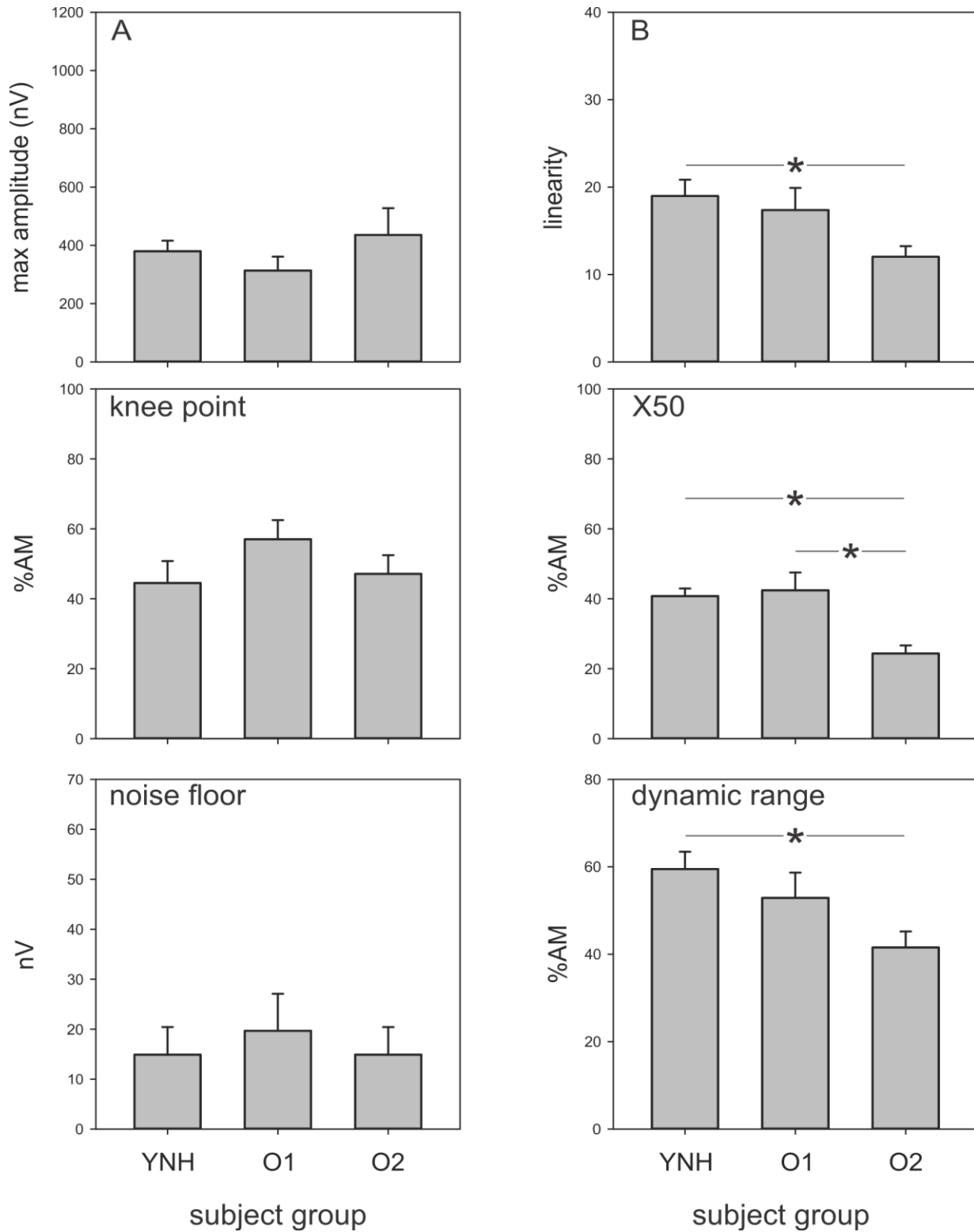
Figure 2. 6: A summary of the modeled parameters of the EFR across the different groups. Error bars are standard error of the mean. Lines with the asterisks represent

A one-way ANOVA was used to examine differences between modeled parameters across the different groups (using all O2 subjects). For the B parameter (linearity) a main effect of group [$F_{(2,33)}=3.5$; $p=0.042$)] was observed and posthoc analysis revealed that YNH had a larger B parameter compared to O2 ($p=0.042$). For the X50 parameter, a main effect of group was observed [$F_{(2,33)}=8.4$; $p=0.001$] and posthoc analysis revealed that YNH had a larger X50 parameter compared to O2 ($p=0.006$) and O1 was larger than O2 ($p=0.002$). For DR, a main effect of group was observed [$F_{(2,33)}=4.0$; $p=0.042$] and posthoc analysis revealed that YNH had a larger dynamic range compared to O2 ($p=0.022$). No differences were observed in the A, noise floor, nor knee point parameters.

Given that the three subjects in O2 group had abnormally large responses, we re-ran comparisons of modeled parameters ANOVAs excluding these three participants. Overall, the effects remained the same except for parameter B such that there was no longer a significant difference between groups ($p=0.07$). The X50 parameter still showed a significant group effect ($F_{(2,30)}=5.9$; $p=0.007$) with posthoc analyses showing that the O2 group had smaller X50's compared to both YNH ($p=0.020$) and O1 ($p=0.009$). The DR still showed a significant group effect [$F_{(2,30)}=3.3$; $p=0.049$] with posthoc analyses showing that the O2 group had a smaller DR compared to YNH ($p=0.040$).

Modeled Parameters Correlations with age:

Pearson correlations were performed between each of the fitted parameters and ages of the subject. Significant correlations were observed between: age and B ($r=-0.36$ $p=0.033$), age and X50 ($r=-0.38$ $p=0.020$) and age and DR ($r=-0.39$ $p=0.018$), all shown in Figure 7. No significant relationships with age were observed for A, noise floor, nor knee point parameters.

28
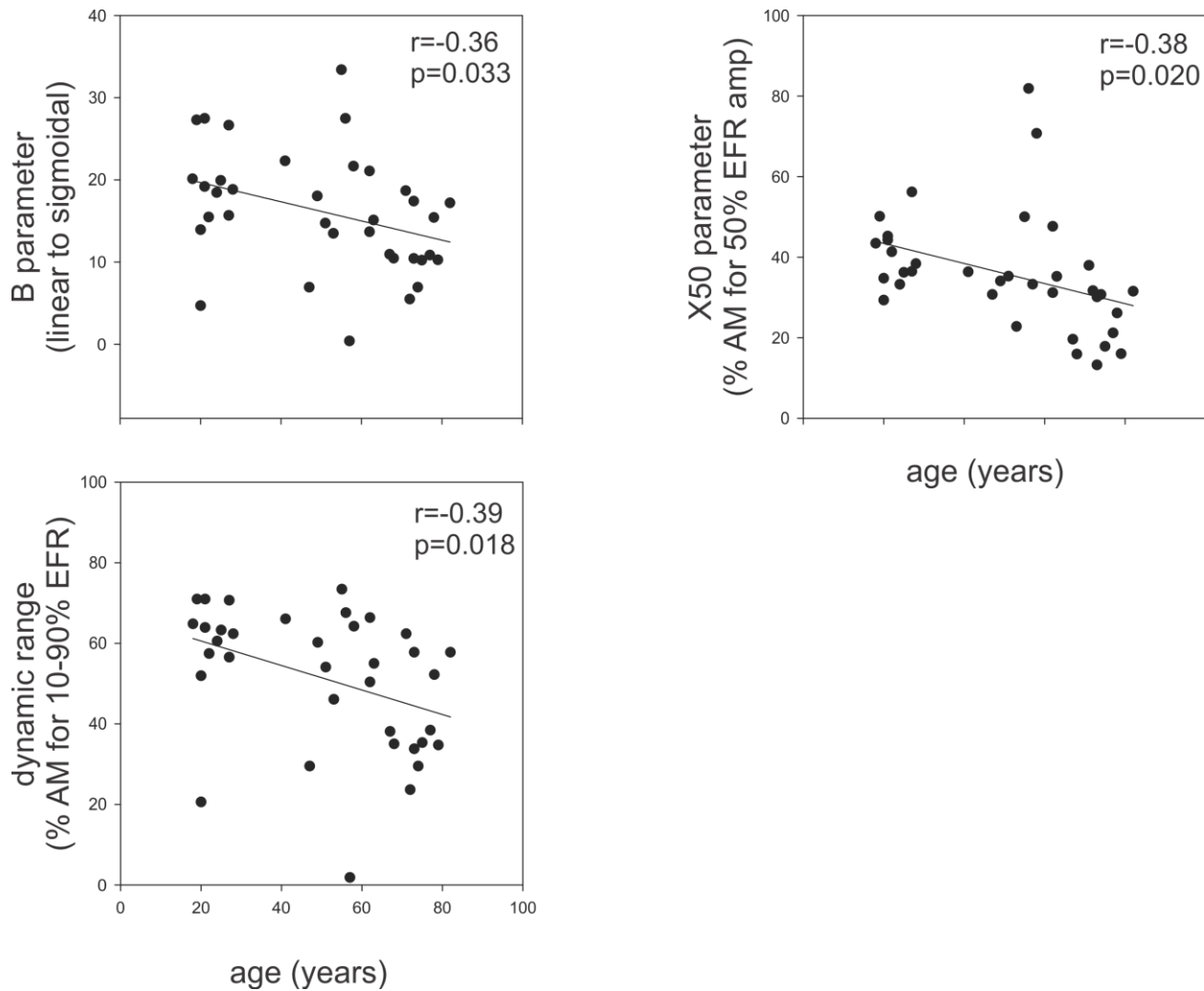
Figure 2. 7: Scatter plots relating the age of subjects to the different modeled parameters. Only significant relationships were plotted.

Relationship between Behavioral AM Detection and EFR amplitude:

Mean EFR AM depth thresholds were similar to the behavioral AM detection thresholds (see Table 1): YNH (behavioral: 11.5%, EFR: 9.1%); O1 (behavioral: 14.3%, EFR: 11.9%); O2 (behavioral: 14.9%, EFR: 11.3%). A significant correlation between thresholds for AM behavioral detection and EFR threshold was observed (r=0.48 p=0.003) Figure 8 shows individual data points and the linear correlation.

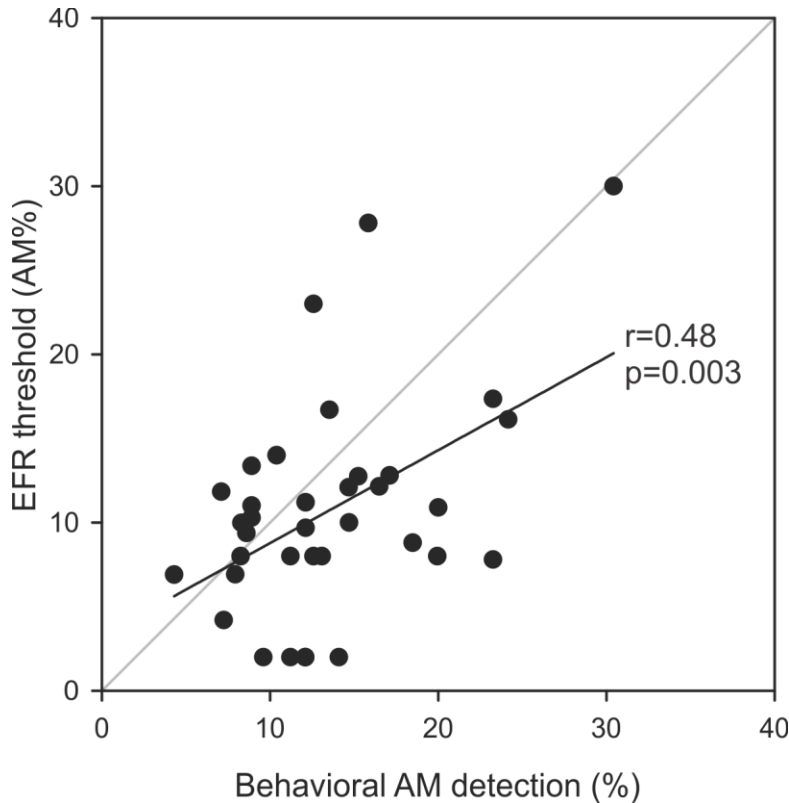**Figure 2. 8: A scatter plot showing a significant correlation between EFR threshold (%AM) and behavioral threshold (%AM). AM indicates amplitude modulation; EFR, envelope following response.**

Sweep EFRs - Phase

In addition to amplitude, the phase of the EFR was examined. Figure 9 shows the EFR phase for all three experimental groups. The YNH group showed a plateau-like response in phase with varying depth of AM whereas the two older groups both showed a negative slope indicating that phase decreased as a function of AM depth. A one-way ANOVA indicated a significant group effect for phase slope [$F(2,33)=1.7$; $p=0.045$] and posthoc analysis revealed that the YNH group's phase slope (-0.05 ° / AM%) was significantly greater (more flat) than the O2 group (phase slope: -0.28 ° / AM%; $p=0.020$). Although the O1 group's phase slope (-0.24 ° / AM%) was numerically steeper than the YNH group, this difference failed to reach significance ($p=0.052$). No group differences were observed for the intercept.
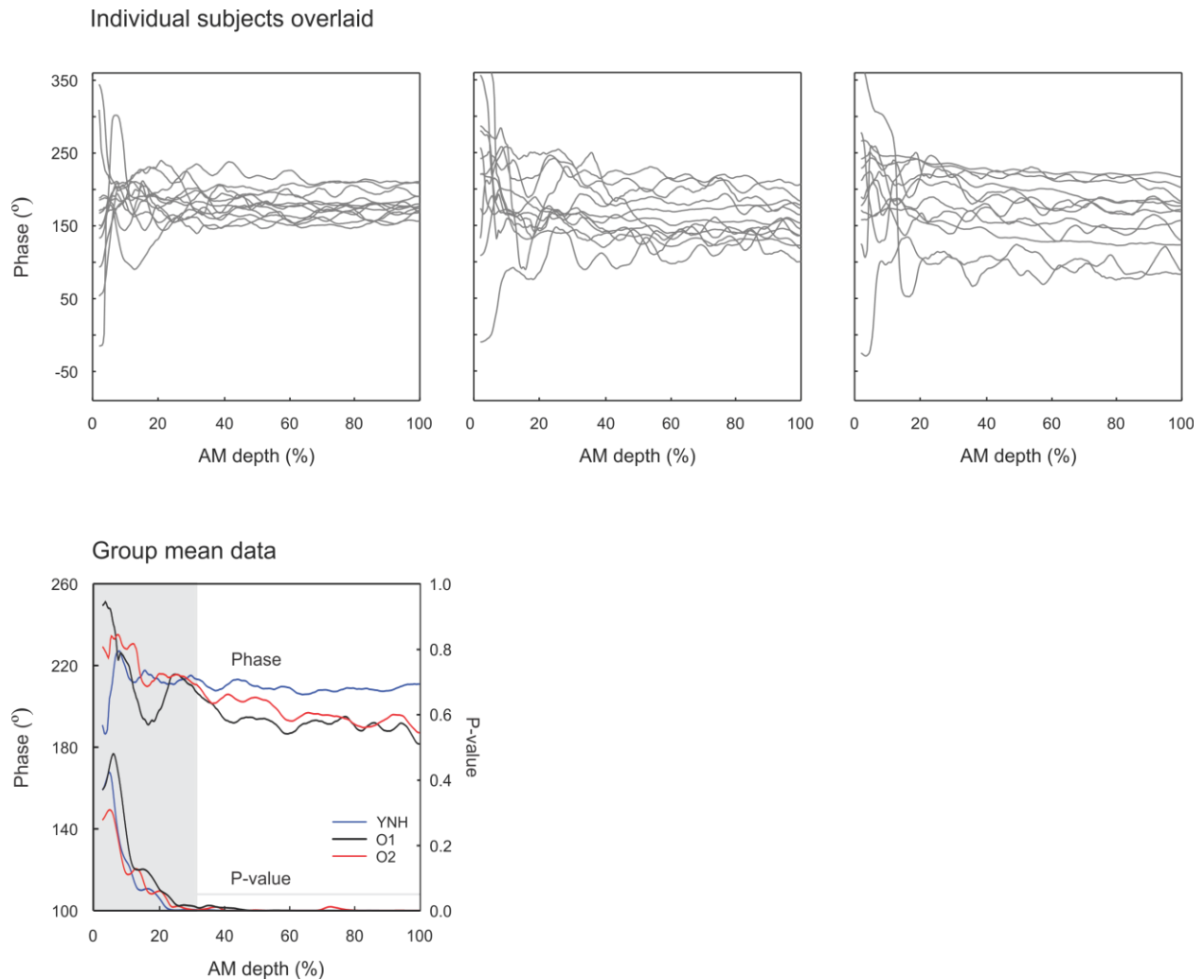
Figure 2. 9: EFR phase as a function of %AM depth for all three groups. The top panel shows all subjects overlaid (gray) for the YNH (left), O1 (middle), and O2 (right) groups. The group mean data is shown on the bottom left. The group average plot also shows the associated p values as a function of AM depth. The gray region depicts an AM depth where the responses were significant (p < 0.05). The gray horizontal line indicates the p = 0.05 level. Note that for YNH subjects, the phase versus AM depth function is relatively flat, whereas for the two older groups, the phase decreases with increased AM depth. AM indicates amplitude modulation; EFR, envelope following response; O1, first older group; O2, second older group; YNH, young normal-hearing group.

In order to help understand the functional significance of these phase-slope differences, we assessed the bivariate relationship between phase-slope and age, hearing thresholds, and AM% detection thresholds. Significant bivariate correlations with phase slope were observed for and age ($r=-0.37$; $p=0.028$), pure tone threshold at 2 kHz ($r=-0.41$; $p=0.015$), and pure tone threshold at 4 kHz ($r=-0.59$; $p<0.001$). No significant correlations were observed for AM%

detection threshold. Age, 2 kHz threshold, and 4 kHz threshold, were entered as predictors of phase-slope difference in a multiple linear regression models. We observed a significant overall model R=0.60, [$F_{(2,32)}=6.1$; p=0.002)]. Among the three predictors, only 4 kHz threshold emerged as a significant independent predictor in the model (semi-partial correlation = -0.42; p=0.005).

Sweep EFR versus ASSR at fixed AM depth:

To compare whether sweep EFR amplitude values were similar to traditional ASSRs recorded at fixed depths, we extracted the EFR amplitude values corresponding to the same AM depths for which we had "fixed AM depth" ASSR data (100, 75, 50, and 25%). Paired t-tests showed that there were no statistically significant differences were seen between fixed and EFR values. Mean values are shown in Table 2.

Table 2. 2: A comparison between sweep EFR amplitudes and fixed AM depth ASSRs are shown

	Sweep EFR (nV) to AM depths				Fixed ASSR (nV) to AM depths			
Group	100%	75%	50%	25%	100%	75%	50%	25%
YNH	344 (157)	299 (128)	245 (81)	135 (55)	357 (144)	308 (95)	254 (80)	138 (47)
O1	263 (109)	225 (110)	187 (87)	116 (50)	281 (144)	249 (94)	195 (104)	112 (50)
O2	985 (330)	357 (303)	325 (292)	272 (224)	391 (310)	365 (313)	344 (298)	228 (226)

Because the sweep EFR data is continuous, portions of the function corresponding to the same AM depths as the fixed AM depth ASSR were extracted. Note that these data include the three subjects with high amplitude ASSRs for the O2 group. SDs are shown in parenthesis.
AM, amplitude modulation; ASSR, auditory steady-state response; EFR, envelope following response; O1, first older group; O2, second older group; YNH, young normal-hearing group.

Discussion

The results of this study revealed four findings: (1) EFRs to sweep AM depth stimuli can be recorded and provide amplitude measures comparable to ASSRs recorded at fixed AM depths. (2) The minimum AM depth for which an EFR can be elicited is related to behavioral AM detection. (3) Aging does not necessarily affect the overall amplitude of the brain's response to AM stimuli but rather differences are apparent in the relationship between AM depth and EFR, such that the responses were more nonlinear and resulted in smaller dynamic ranges compared to younger adults. (4) The phase of EFR did not change as a function of AM depth for the young normal hearing controls but did for the older group.

The EFR technique as a correlate of neural AM depth coding and behavior:

The results of the current study showed that sweep EFR amplitudes are remarkably similar to ASSRs recorded at the same fixed AM depth, and no significant differences were observed between the two response types (Table 2). Using "sweep" stimuli (termed "zoom" or "ramped" stimuli by others), for which a non-stationary ASSR (i.e., EFR) has been recorded to a "changing" stimulus, has previously been reported for intensity changes (Linden et al. 1985, Rodriguez et al. 1986, Picton, van Roon & John 2007) and AM rate changes (Purcell et al. 2004, Poulsen, Picton & Paus 2007, Poulsen, Picton & Paus 2009). The present study adds to the current body of knowledge and demonstrates that non-stationary ASSRs (or EFRs) can also be reliably recorded to varying AM depth. Previous work examining ASSRs at various AM depths have reported linear (Kuwada, Batra & Maher 1986) or non-linear (Ross et al. 2000, Rees, Green & Kay 1986, Picton et al. 1987) relationships. Our data suggests that the degree of linearity varied across the different subject groups, quantified by the B factor where smaller values of the B result in steeper slopes

and non-linearity at high modulation depths where the function saturates. In YNH, the EFR-AM depth function had larger B values, indicating a more linear and shallower slope with less saturation compared to the O2 subjects.

In young normal hearing subjects, Picton et al. (1987), used a 1000 Hz carrier tone with 39 Hz AM and found behavioral AM depth thresholds were on average 5% while ASSR depth thresholds were almost the same at 4.9%. We also found very similar thresholds between behavior and EFR: for YNH, behavioral was 11.5% and EFR 9.1%. The overall values of the AM differed from Picton et al., (1987), i.e., near 5% and 10% are likely due to our use of a white noise carrier. A weak (r=0.48) but statistically significant (p=0.003) correlation was observed between behavioral AM detection and EFR thresholds (see Figure 8). Although noise carriers and tones may produce different results, a likely reason for our low correlation is that there was not sufficient variation in behavioral AM detection thresholds across subjects. The inclusion of patient populations such as auditory neuropathy with known elevated AM detection thresholds (Zeng et al. 2005a) would likely strengthen the relationship. The current study has provided both theoretical and practical bases for undertaking such an investigation.

Effects of aging on the EFR

The results of the current study showed that aging does not change the overall amplitude of the EFR but rather affects the shape of the EFR amplitude versus AM depth function. Three parameters (i.e., B, x50, and DR) were shown to be related to aging not only by demonstrating significant group differences (Figure 6) but also significant correlations with age (Figure 7). The "B" parameter and DR are related. B is inversely related to the slope of the sigmoidal function: small values result in a rapid amplitude change to maximum peak values whereas high values show

a more gradual change to peak amplitude values. "DR" is a measure of how effectively the auditory system is able to differentiate between different AM depths. For example, a very low DR functionally translates into an "all or none" type of neural encoding of AM depth, whereas a high DR captures the response amplitude changes to varying depths of AM. Reduced X50 in the older O2 group was also observed suggesting that neural populations encoding AM saturate earlier with aging.

It is not clear why the knee point (AM depth for saturation) did not differ between groups. One can speculate how these parameters are related to human hearing and specifically performance in both quiet and noise. Normal speech is composed of varying degrees of AM depth with varying AM rate (Rosen 1992). The addition of noise effectively reduces the depth of AM by filling in the "valleys" in the speech envelope. A reduced neural DR for AM encoding would effectively decrease speech intelligibility by obscuring subtle differences in amplitude fluctuations in speech. This phenomenon may be related to the perceptual difficulties with speech perception in noise the elderly often report when listening in challenging environments (Pichora-Fuller, Souza 2003).

A recent review by (Bharadwaj et al. 2014) posits that "cochlear neuropathy", also referred to as "hidden hearing loss" is thought to play a role in aging (Plack, Barker & Prendergast 2014), through selective loss of low spontaneous rate auditory fibers and leading to impaired speech perception in noise. Bharadwaj suggests that use of ASSRs to AM stimuli of varied depth may reveal differences associated with "cochlear neuropathy" since high spontaneous rate auditory nerve fibers would be saturated, leaving only low spontaneous rate fibers to encode the modulation. These fibers are mostly responsible for suprathreshold coding. The reduced DR we observed with aging is consistent with a reduction in the number of neurons being able to encode

intermediate AM depths. One important caveat is that we did not measure speech perception in quiet or noise. Caution is warranted when relating these parameters to speech perception.

A limited number of studies have examined ASSRs as a function of AM depth in older listeners. (Leigh-Paffenroth, Fowler 2006) examined 20, 40 and 90 Hz ASSRs to 500 and 2000 Hz tone carriers with various AM depths (10%, 20%, 50%, 80% and 100%) in older subjects (mean age 70 years). The ASSR was quantified using phase locking measures to the modulation. For 40 Hz, older subjects had fewer phased-locked 500 Hz responses compared to younger controls and this reduction was related to speech perception measures. (Boettcher et al. 2001) examined, in older adults and young controls, carriers of 520 Hz and 4000 Hz modulated at 40 Hz with AM depths ranging from 5% to 100%. No differences in amplitudes were found between the two groups. Our results are similar to Boettcher et al., (2001) in that no amplitude differences were seen between the older groups and YNH (with the exception of the three subjects with abnormally large responses). Additionally, we found differences the EFR function versus AM depth using our finer resolution AM stimuli. Relating our current findings to (Leigh-Paffenroth, Fowler 2006) is difficult because of differences in stimuli and assessment metrics, and we did not assess speech perception.

It remains unclear why some O2 subjects had atypically large EFR amplitudes. The other fitted parameters of their modeled data were in the normal range except for the maximum amplitude. Hearing levels, audiogram shape and AM depth detection thresholds were also in normal ranges for the O2 group. The large amplitudes may be related to common generator of the 40 Hz ASSR and the auditory middle latency response P1 (Bohórquez, Özdamar 2008). Some previous work has suggested that P1 may be larger with aging (Woods, Clayworth 1986, Alain, McDonald 2007), although this would not account for why the other O2 subjects did not differ

from YNH. A follow-up study examining the different EFR-AM depth fit parameters to other behavioral measures such as speech perception is warranted.

Phase of EFR

The phase versus AM depth function (phase-slope) was relatively flat in the YNH group but was negative in the older groups (figure 9). Modulation depth versus ASSR functions are much less studied than intensity versus ASSR functions and therefore interpretation of what these functions represent is less straightforward. Intensity functions often show reduced amplitudes and prolonged latencies with lower level sounds (Picton, van Roon & John 2007). The latency (or phase) change with intensity is thought be related to acceleration of the rise time of the stimulus envelope (Heil 1997). With progressively less AM depth, there would be shallower AM envelopes which would predict longer latencies. However, when responses were detectable in the YNH group, phase/latency remained relatively constant. With the older groups, phase/latency decreased with increasing AM depth. There is limited published data on the phase of the 40 Hz ASSR as a function of AM depth and carrier frequency. In YNH subjects, using pure tones ranging from 500 to 4000 Hz, (Picton et al. 1987) found very little change in phase as a function of AM depth. Conversely, (Ross et al. 2000) found systematic deceases in the ASSR phase as a function of AM depth using MEG recordings for a 250 Hz carrier (40 Hz AM). In animals, little change in phase has been observed in the inferior colliculus with decreasing AM depth (Brugge, Blatchley & Kudoh 1993). In the present study, the underlying reasons for the differences in phase slope versus AM depth between young and older groups is not entirely clear. In the current study, white noise was used as a carrier and therefore there are contributions from both high and low carrier frequency coding neurons that sum together to yield a composite EFR recorded at the scalp. In the older groups, the EFR has a relatively large low frequency carrier component because of their high

37

frequency hearing loss. In fact, the phase-slope with AM depth was significantly related to pure tone thresholds at 4 kHz. This would suggest that the phase slope differences in the older group are driven by low frequency carriers, perhaps at or below 250 Hz given that Ross et al. (2001) observed phase differences with this carrier in YNH listeners. ASSRs to high frequency carriers have an earlier latency compared to low frequency carriers for cortical ASSRs (Stapells et al. 1984, Cohen, Rickards & Clark 1991). If the overall response (from 2% to 100% AM) were dominated equally by high and low carriers, then the entire EFR versus AM depth function would be shifted for the older group compared to YNH. Instead, the divergence between the YNH and older groups occurred at AM depths above ~40% (thus leading to a slope difference). This data therefore suggests that AM coding at high AM depths (above 40%) is impacted substantially by high frequency carriers, whereas low modulation depths elicit normal (young-like) responses when low frequency carriers are dominant. Further studies examining the role between low and high carrier frequency contributions are warranted. Age is not likely driving this effect given that the partial correlation of age was not significant in the multiple linear regression analysis.

Conclusion

The results of the current study reveal the following findings: swept AM depth stimuli can elicit robust responses similar to fixed depth stimuli, the EFR AM depth thresholds were related to behavioral measures of AM depth detection, the shape of the EFR function differed with age with elderly subjects having reduced DRs. The current study has established a solid foundation for the application of the swept AM depth approach to the auditory neuropathy population in which a larger range of AM detection thresholds would be expected.

ACKNOWLEDGMENTS

CHAPTER 3

Using Envelope Following Responses to Amplitude Modulation to Assess Temporal Acuity in Auditory Neuropathy

ABSTRACT

OBJECTIVE: To record Envelope Following Responses (EFRs) to monaural amplitude-modulated broadband noise carriers in which amplitude modulation (AM) depth or frequency modulation (FM) rate was gradually varied over time and to compare these objective electrophysiological measures to subjective behavioral thresholds in normal-hearing and hearing-impaired individuals with auditory neuropathy.

DESIGN: Participants: different groups of subjects included normal hearing group, older group with different types of hearing loss and individuals with auditory neuropathy. Electrophysiology: In condition 1, the AM depth (fixed FM=41 Hz) of a white noise carrier, presented at a highest comfortable level intensity, was continuously varied from 2% to 100%. EFRs were analyzed as a function of the AM depth. In condition 2, the FM rate (fixed AM=100%) of a white noise carrier, presented at a highest comfortable level intensity, was continuously varied from 2 to 300 Hz. EFRs were analyzed as a function of the AM depth or FM rate. Psychophysics: A three alternative, forced-choice procedure was used to track the amplitude modulation (AM) depth needed to detect AM at 41 Hz (AM detection). Also, temporal modulation transfer functions at different modulation rates (2 Hz to 2 KHz) were obtained for subjects who participated in the second condition.

RESULTS: AN subjects had higher significant behavioral AM detection thresholds than matched thresholds hearing impaired subjects. A significant correlation (r=0.89) were observed between behavioral and physiological AM detection thresholds. EFRs from both groups were fitted with a sigmoidal function. Not all AN subjects had a perfect sigmoidal fit. The shape of the function differed across groups. The AN group reached EFR peak amplitude at significantly lower magnitude than the NH group and had a narrower neural dynamic range. Fluctuated EFR profiles were observed in some AN subjects.

CONCLUSIONS: The present study introduced a novel electrophysiological method to assess temporal acuity objectively. EFRs were recorded as a response to different stimuli (swept-AM depth and swept-FM rate). Sweep recordings may provide additional valuable information at suprathreshold intensities including the plateau level, slope and dynamic range. AN subjects had a reduced neural dynamic range compared to normal hearing subjects suggesting that neuropathy affects the ability of the auditory system to encode subtle differences in the depth of amplitude modulation. The behavioral-physiological AM depth threshold relationship was significantly high which make it a considerable testing method to be clinically used to measure temporal processing deficits in individuals with auditory neuropathy.

Introduction

Understanding speech depends on the listener's ability to extract and process temporal envelope information (Shannon et al. 1995). Since Individuals with auditory neuropathy (AN) have a significant temporal processing deficit, it is difficult for them to understand speech despite the fact that they can detect the sound (Zeng et al. 1999). Gap detection and temporal modulation transfer function (TMTF) are often used to measure the severity of temporal processing impairment (Zeng et al. 1999). However, these tests rely on subjects' active responses to stimuli, making them difficult, if not impossible, for infants and patients with cognitive disabilities. It is crucial to find an alternative task that can reliably and objectively measure temporal acuity.

Auditory evoked potentials (AEP) provide diagnostic methods that have been used to assess hearing thresholds for infants. The auditory brainstem response (ABR), which is a form of AEP characterized by its transient response, is an objective diagnostic test that is commonly used in the newborn hearing screening tests in the US. The auditory steady-state response (ASSR), which is another form of AEP characterized by its periodicity that tracks the evoking stimulus, has also been frequently used to evaluate hearing thresholds in infants (Burkard, Eggermont & Don 2007, Attias et al. 2006). Both of theses objective audiological tests are used mainly to only assess hearing thresholds. However, measuring hearing thresholds is not the only necessity because it does not always reveal all types of hearing disease especially in cases of central auditory processing disorder or AN. Therefore, the envelope following response (EFR), which is an AEP that is intermediate between transient and sustained, has extensively studied to be used to examine temporal acuity (Picton 2013, Purcell et al. 2004, Aiken, Picton 2008, Boettcher et al. 2001, Leigh-

Paffenroth, Fowler 2006, John, Dimitrijevic & Picton 2003, Rodriguez et al. 1986, Linden et al. 1985, Picton 2010).

The uniqueness of our study compared to previous studies is shown in the type of stimuli that was used as well as the population that was tested. We examined the EFR profiles to sweep-AM depth or sweep-FM rate stimulus in individuals with AN to provide an objective measure to evaluate the temporal acuity in infants. Also, our study explored the possibility of using the EFR profile as a biomarker to differentiate between the type of the AN lesion (pre-synaptic vs. post-synaptic). Assessing temporal acuity as well as identifying the type of AN lesion will help clinicians and guardians of AN infants in their decision about the appropriate intervention, especially in the case of cochlear implant candidacy.

Methods

- ## AN subjects

The targeted population of this study is individuals with auditory neuropathy. Ten subjects with hearing loss were recruited to participate in our experiment. Only eight (aged 10-66 years, four females) of the ten recruited subjects were qualified to be included based on our study inclusion criteria. All AN patients who have been included have all of the following characteristics: (1) preserved outer hair cell function based on presence of otoacoustic emissions (OAEs) and/or cochlear microphonics (CMs); (2) absent or abnormal ABRs beginning with Wave I that are beyond what would be predicted by similar cochlear hearing loss; (3) normal tympanometry and brain imaging results.

A total of twelve ears from the eight AN subjects were analyzed. All ears have abnormal pure tone thresholds (above than 20 dB HL) measured at 250, 500, 1000, 2000, and 4000 Hz. This

was assessed using ER3A earphones and a GSI 61 Clinical Audiometer with a 10 dB down/5 dB up bracketing procedure. Table 3.1 contains the data on the AN subjects that include the site of lesion (pre-synaptic vs. post-synaptic), the gene mutation if known, demographics (age, gender), pure-tone threshold average, and behavioral amplitude modulation detection threshold at 41 Hz modulation frequency. Some AN subjects in this study also participated in some other published studies (Zeng et al. 2005b, Michalewski et al. 2009, Dimitrijevic et al. 2011, Wynne et al. 2013). For these AN subjects, we use the same codes to help readers track the progress of their hearing progression.

Two AN subjects are siblings (AN32, AN33) and have heterozygous mutations of *OTOF* which cause their hearing thresholds to elevate significantly when they are febrile (Varga et al. 2006, Starr et al. 1998)

Two AN subjects are children, and new AN codes have been assigned to them for future reference (AN41 and AN42).

Finally, hearing impaired subject with acoustic neuroma who participated in a previous study (Wynne et al, 2013) participated in this study. Similar to other AN subjects, this neuroma subject had an abnormal ABR and elevated amplitude modulation detection threshold.

Table 3. 1 AN subjects info

AN ID	AN Cod	Site of AN	Age	Sex	Ear Tested	OAE	ABR Wave V Latency	PTA (Low) (dBHL)	PTA (High) (dBHL)	AMDT (dB) @41Hz	Gene Mutation	Notes
AN#1	AN32	Synapse	25	F	Left	Yes	Delayed	28	48	-17.33	OTOF	Temp.
					Right	Yes	Delayed	28	43	-16.31		Sensitive
AN#2	AN33	Synapse	21	M	Left	Yes	Delayed	28	52	-17.33	OTOF	Temp.
					Right	Yes	Delayed	38	50	-18.67		Sensitive
AN#3	AN13	Nerve	43	F	Left	Yes	Absent	73	70	-13.33	?	Peripheral
AN#4	AN27	?	27	F	Right	Yes	Absent	95	110	-9.33	?	?
AN#5	AN42	?	12	M	Left	Yes	Delayed	50	83	-14.12	?	AN
	AN42		10		Right	Yes	Delayed	51	75	-14.94	?	new
AN#6	Acoustic-Neuroma	nerve	66	F	Right	No	Delayed	50	80	-12.67		neuroma
AN#7	AN7	?	46	M	Right	Yes	Absent	57	43	-13.33	?	AN
AN#8	AN41	?	14	M	Left	Yes	Delayed	39	66	-13.33	?	Hypoxia, Dyslexia
	AN41				Right	some	Delayed	48	69	-12.33		new

Synapse = ribbon synapse disorder; Nerve = neural AN; OAEs = Otoacoustic Emissions; PTA (Low) = Pure Tone Threshold Average at frequencies range 0.125-2.0 kHz; PTA (High) = Pure Tone Threshold Average at frequencies range 4.0- 12.0 kHz; ? = unknown; OTOF = Otoferlin; AMDT@41Hz= Amplitude Modulation detection threshold at 41 Hz frequency modulation; New= New AN subject has not been identified in previous studies
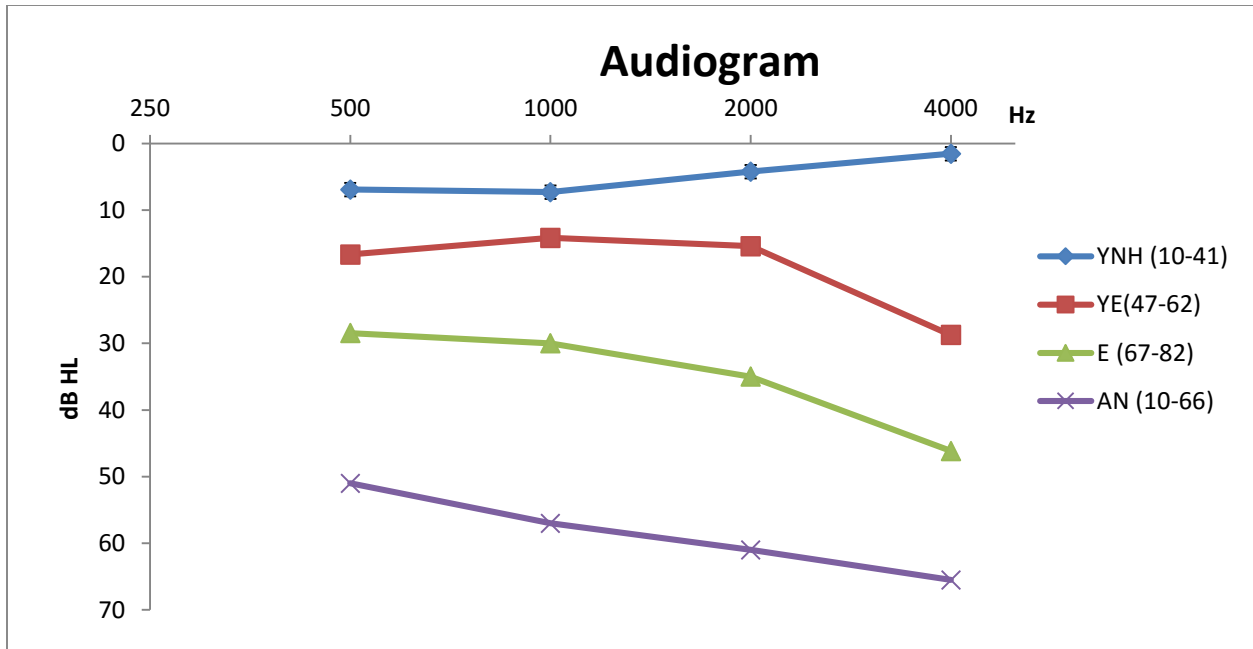
Figure 3. 1 Audiogram shows thresholds for all groups participated in this study and previous study

All experimental protocols have been approved by the Institutional Review Board of the University of California Irvine (HS#2000-1453). Written informed consent has been obtained from each subject and their guardians if they are younger than 18 years old after the nature of the study was explained. Subjects were paid to participate in the study.

- **Control Subjects**

Three groups of subjects, young normal hearing group ("YNH", 18 to 28 years; pure tone average=9 dB HL), a first older group ("O1"; 41 to 62 years; pure tone average=30 dB HL) and a second older group ("O2"; 67 to 82 years; pure tone average=49 dB HL), whose data were previously reported (Dimitrijevic et al., 2016), served as a control in this study.

Also, we included two normal hearing children to serve as a control for AN children. One of the normal children is a twin to one of the AN subjects (AN41) and, therefore, can serve as an ideal control

Table 3. 2 Control Subjects info

Control	Age	N, Gender	Ear Tested	OAEs	ABR Wave V Latency	PTA (Low) (dBHL)	PTA (High) (dBHL)	comments
Normal children	10-14	2,M	Right	Yes	Not measured	5	5	To serve as control for 2 AN children
Normal Adults	18-41	6, M &7,F	Right	Yes	Not measured	7	4	From chapter 2 (Dimitrijevic et al, in press)
Older	47-63	7,M & 4,F	8R &3L	Yes	Not measured	16	30	From chapter 2 (Dimitrijevic et al, in press)
Elderly	67-82	8,M & 4,F	1R &1L	-	Not measured	34	50	From chapter 2 (Dimitrijevic et al, in press)

SNHL = low-frequency sensorineural hearing loss control; Neuroma = acoustic neuroma control; OAEs = Otoacoustic Emissions; PTA (Low) = Pure Tone Threshold Average at frequencies range 0.125-2.0 kHz; PTA (High) = Pure Tone Threshold Average at frequencies range 4.0- 12.0 kHz.

- **Study Design:**

We measured both psychophysical amplitude modulation detection thresholds and electrophysiological envelope following responses. For the psychophysical tasks, amplitude modulation detection thresholds were obtained for all subjects at a single modulation rate (41 Hz). Additionally, temporal modulation transfer functions at different modulation rates (2 Hz to 2 KHz) were obtained for five of these subjects. For the electrophysiological measures, EFRs were obtained for all subjects in response to an *amplitude-modulated* stimulus (swept modulation depth). Additionally, for six AN subjects EFRs were measured for one or both of two *frequency-*

modulated stimuli (swept modulation rate; 2-59 Hz and/or 62-300 Hz). Figure 3.2 summarizes the block diagram for the study design. Psychophysically-measured amplitude-modulation detection thresholds were compared with thresholds found using the EFR. Thresholds at a single modulation frequency, temporal modulation transfer functions, and EFR results were compared between AN subjects and control subjects.
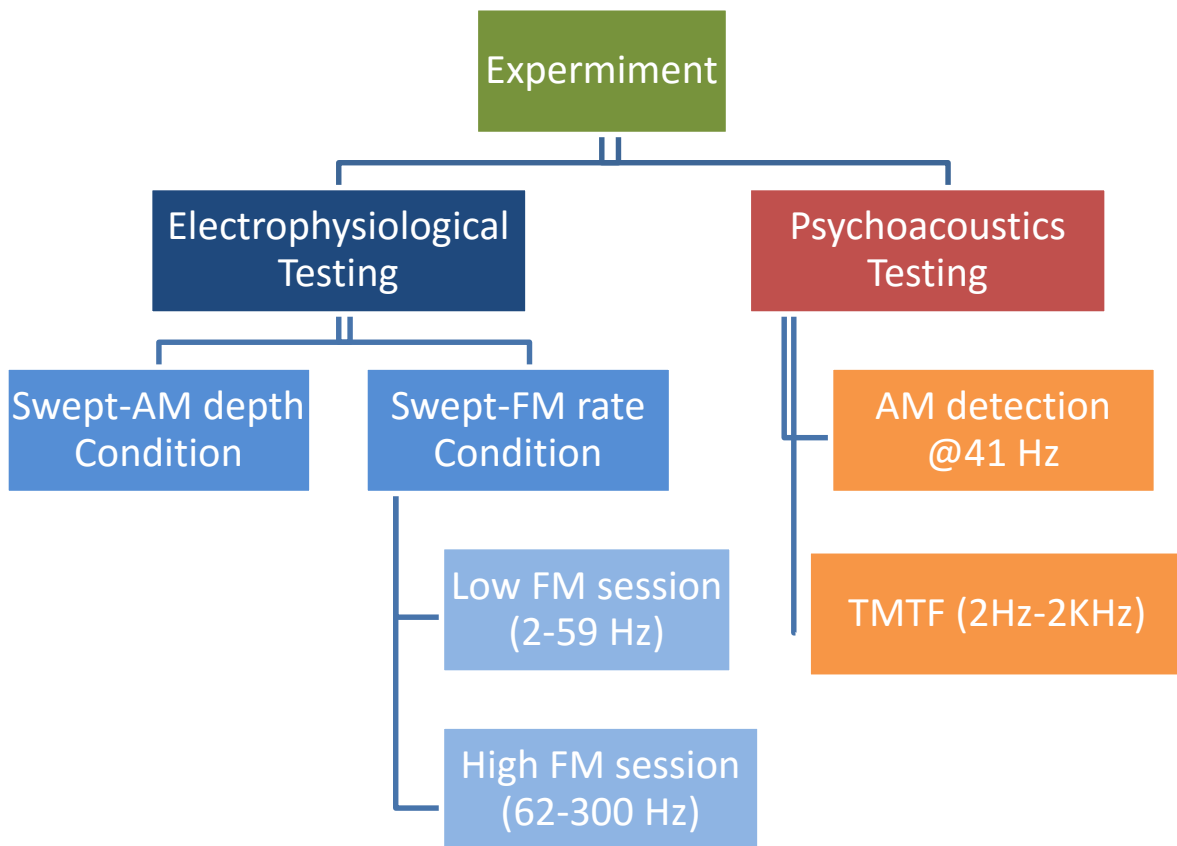

Figure 3. 2 Visual diagram for study design

- **Stimuli**

For the electrophysiological testing, the stimulus differed between two conditions (i.e. amplitude vs. frequency modulation). In the first condition, called *swept-AM depth*, envelope following responses (EFRs) were measured in response to an amplitude-modulated stimulus with

swept AM depth and fixed modulation rate (41 Hz). In the second condition, called *swept-FM rate*, EFRs were measured in response to a frequency-modulated stimulus with swept FM rate and fixed modulation depth (100%). Both stimuli were generated using a MASTER research system (John, Picton 2000, Purcell et al. 2004). In both stimuli, the carrier was white noise.
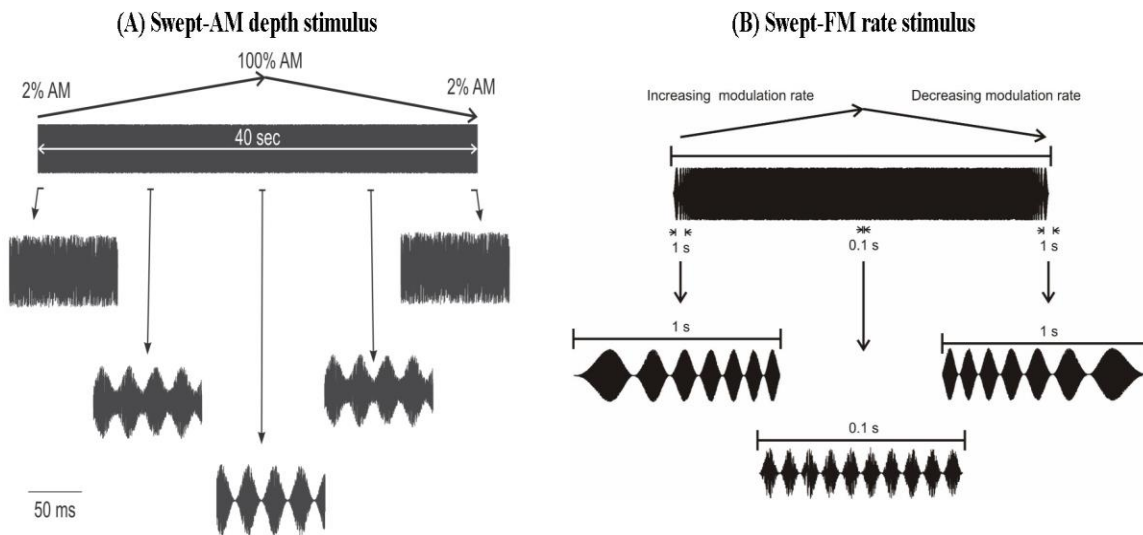
Figure 3. 3 Electrophysiological testing stimuli

In the swept-AM condition, at least three trials were recorded. Each trial comprised of 30 sweeps and lasted 20.48 min, for a total recording time of slightly over an hour. The stimulus modulation depth was swept from 2% to 100% across each stimulus sweep, which was partitioned into 40 epochs. The AM depth was linearly increased during the first 20.48 seconds (20 epochs) and then decreased with the same pattern over the remaining of the second 20 epochs. The amplitude modulation depth sweep rate was 4.785% per second. Each stimulus was presented monaurally at the most comfortable level (Table 3.3). Stimuli were calibrated using the

unmodulated carrier with a Brüel & Kjær (Investigator 2260) sound level meter and a 2cc coupler DB0138 set simulator coupled to an Etymotic ER3A earphone acoustic transducer.

Table 3. 3 Summary of the pure-tone audiograms and AM detection thresholds for both behavior and EFR

		Pure tone threshold (Hz)				AM threshold (%) Behavioral	Stimulus Intensity (dB SPL), range
Group	Age	500	1000	2000	4000		
YNH	22(6)	8(8)	8(5)	5(8)	2(6)	11.7(4)	68
O1	55(7)	17(14)	14(11)	15(15)	29(15)	12.8(3.9)	71(4), 78-67
O2	75(6)	31(19)	33(17)	38(17)	50(28)	14.6(6.5)	81(6), 73-93
Acoustic Neuroma	66	55	70	50	65	23.3	93
AN	21(9)	51(26)	57(23)	61(29)	65(28)	25.8	78(7), 62-88

SDs are shown in parenthesis.

For the swept-FM condition, we assessed the temporal processing by presenting an AM stimulus that varied in modulation rate as a function of time. As in Purcell et al (2004), the stimulus was a broadband noise carrier that was generated using a MASTER research system (John, Picton 2000) and was modulated at a fixed amplitude depth (100%).

There were two separate recording sessions for the swept-FM condition. In the 1st recording session (*low-frequency session*), we assessed the envelope following response to low-frequency modulation rate, which varied from 2 to 59 Hz over time. In the 2nd recording session (*high-frequency session*), we assessed the envelope following response to a relatively higher frequency modulation rate that varied from 62 to 300 Hz over time. In the low-frequency session,

a sweep consisted of 40 epochs, whereas in the high-frequency session, a sweep consisted of 30 epochs. In the low-frequency modulation recording session, we used a frequency modulation rate that increased linearly for the first 20 epochs from the minimum (2 Hz) to the maximum (59 Hz), then decreased in a reverse pattern from 59 to 2 Hz for the remaining 20 epochs. In the high-frequency modulation recording session, the frequency modulation rate was increased linearly from the minimum (62 Hz) to the maximum (300 Hz) for the first 15 epochs (15.36 sec), then decreased in a reverse pattern for the remaining 15 epochs. Both recording sessions was comprised of three trials with 30 sweeps in each trial. Total recording time was 61.5 min for the low-frequency-session whereas the total recording time was 46.08 min for the high-frequency-session.

Experimental Procedures

- **Psychophysical task**

In the psychoacoustics test, we measured the behavioral modulation thresholds using a custom MATLAB program. We utilized a three-alternative forced choice (3AFC) tracking method to determine the behavioral thresholds in different modulation frequencies. We tested the same ear that was tested in the electrophysiological test monoaurally. During each trial, three sounds were played sequentially, including a sinusoidally modulated noise and two unmodulated standards. The three sounds were presented in random order. The listener was required to identify the sound that contained the modulated noise and was provided with feedback indicating whether or not the choice was correct. Two consecutive correct responses would reduce the modulation depth whereas any incorrect response would increase the modulation depth. Reversals occurred when a subject went from two consecutive correct responses to an incorrect response, or from an incorrect response to two consecutive correct responses. A large step size (50% change) was used for the

51

first four reversals and then a smaller step size (20% change) was used for the remaining reversals. The test was terminated after 12 reversals.The threshold was calculated as the mean of the last eight reversals, producing a 70.7% correct response. For all subjects, amplitude modulation threshold was assessed at 41 Hz rate. Thresholds at this modulation frequency were correlated with objective threshold obtained in the electrophysiological testing.

- **Physiological Response Recording and Analysis**

The swept-AM condition, as well as low modulation session of the swept-FM condition, was recorded in a similar way that was discussed in chapter two of this dissertation. Please refer to **Stimulus Presentation and Physiological Response Recording and Analysis section** of chapter two for more details. For the high modulation session of the swept-FM condition, we changed the pass-band to 10Hz -1KHz instead of 0.3-300 Hz and used an estimated physiological delay of 10 ms instead of 30 ms to improve alignment between the reference and response waveforms during the analysis (Aiken & Picton 2006).

- **Statistical analysis**

ANOVA, as well as post-hoc t-tests, were used to compare behavioral performance between different groups. Pearson correlation was used to relate the amplitude modulation detection threshold to thresholds measured electrophysiologically. The behavioral measures included (a) the pure-tone threshold average (dB HL) from 500 to 4000 Hz in octave step, (b) the amplitude modulation threshold at 41 Hz modulation frequency, (c) the maximum frequency (Hz) at which 100-Hz amplitude modulation could be perceived by the participant. The EFR measures included (a) the amplitude modulation depth (%) at which the response became statistically

significantly different ($p<0.05$) from the noise floor, (b) the maximum EFR frequency (Hz) at which the response became no longer significant from the noise floor.

To quantify the EFR, we modeled the EFR magnitude versus AM depth results as a sigmoidal function:

$$EFR\ magnitude = Noise + \frac{A}{(1 + e^{\frac{-(AM\ depth - x50)}{B}})}$$

In which, A was the peak value of the EFR magnitude, B was reversely related to the slope of the EFR function, X50 was the AM depth at which the EFR magnitude was half of the peak value, Noise estimated the noise floor of the EFR.

Results

- **Behavioral Results**

On average, compared with the controls, auditory neuropathy subjects showed elevated behavioral hearing thresholds. The AN subjects also produced significantly elevated amplitude modulation detection thresholds at 41 Hz modulation frequency (figure 3.4).
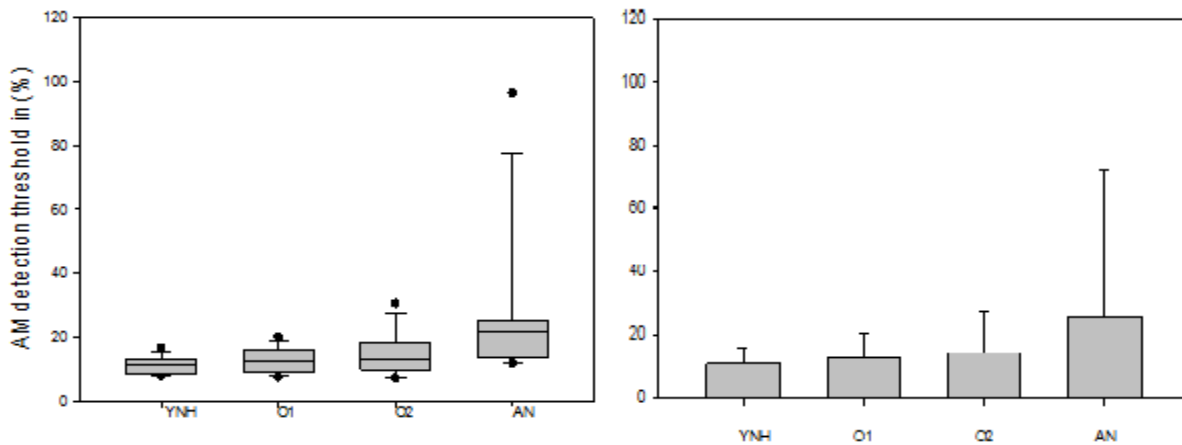
Figure 3. 4 Behavioral AM threshold at single modulation rate (41 Hz)

To isolate the role of hearing loss, Figure 3.5 and 3.6 shows a comparison between subjects from two different groups with approximately same hearing thresholds: (1) five AN subjects and (2) five cochlear-impaired subjects with matched pure tone threshold average. Independent of the degree of hearing loss, the AN subjects produced significantly elevated modulation detection thresholds.
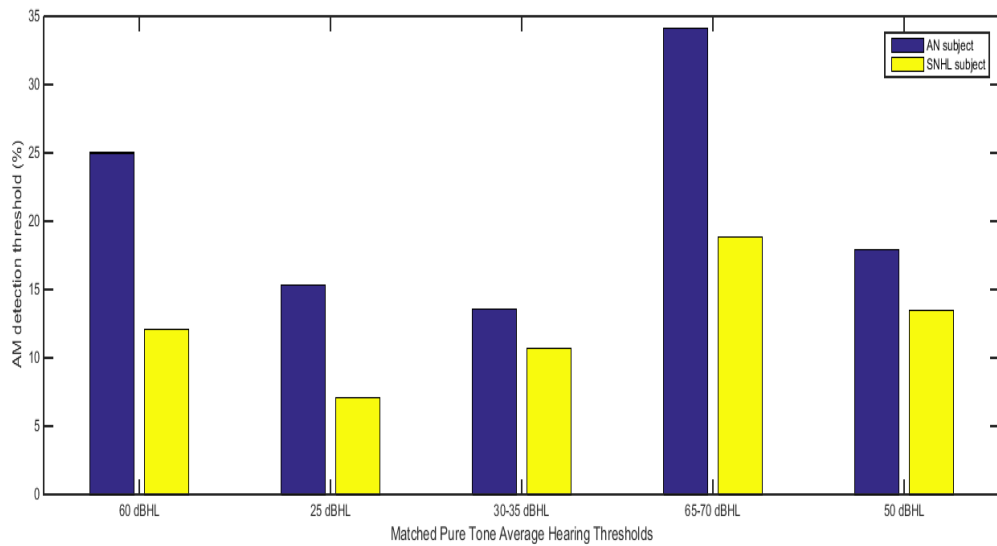
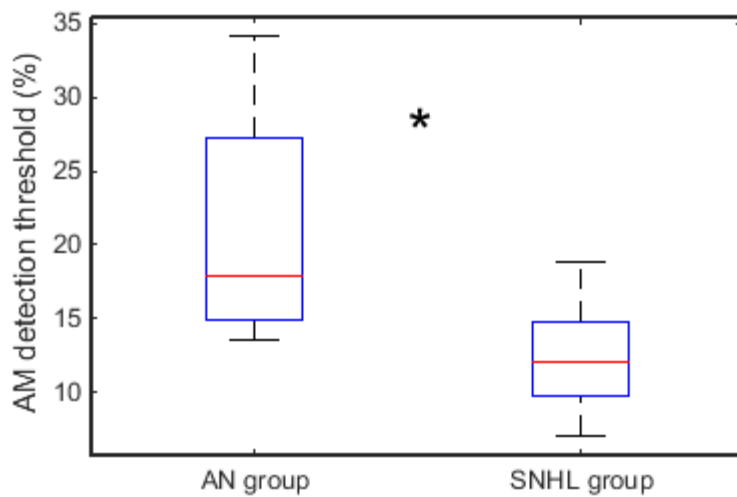**Figure 3. 5 AM detection threshold for AN Vs. SNHL with same hearing thresholds**

Figure 3. 6 Grand Average AM detection threshold (AN vs. SNHL) groups. Asterisks represent significantly different comparisons (P<0.05)

Figure 3.7 shows the TMTF between the AN child and his normal control twin, with the latter having better modulation detection thresholds at modulation frequencies between 64 and 512 Hz.
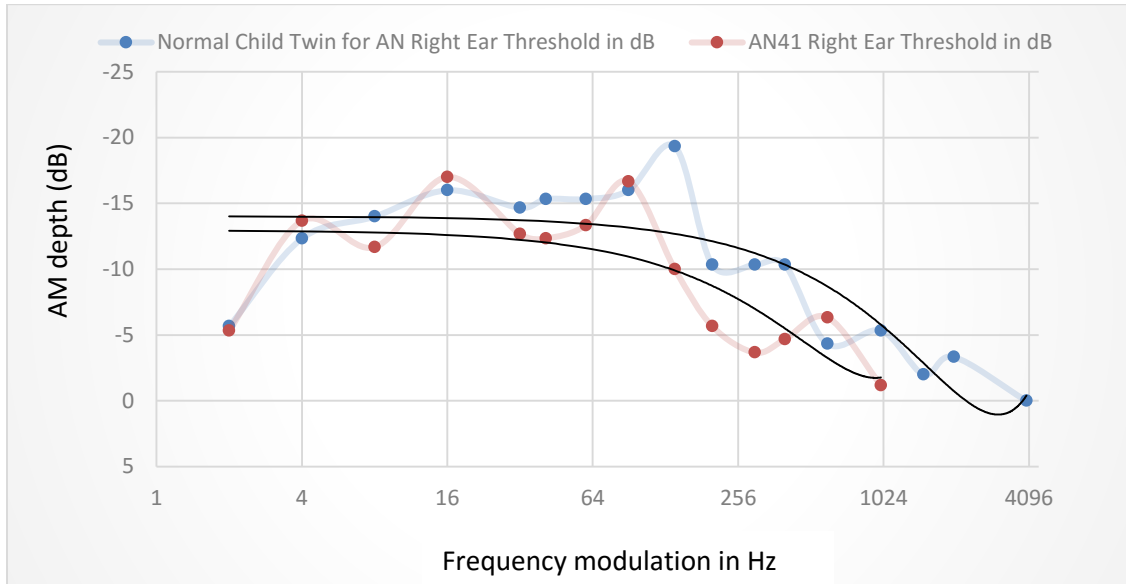
Figure 3. 7 TMTF for AN child Vs. his twin Control

- **Electrophysiological Results**

Figure 3.8a shows a significant correlation in all subjects between behavioral amplitude modulation detection thresholds and electrophysiological thresholds from the EFR (r=0.89; p<0.01). A less correlation but significant (r=0.65; p<0.01) is also shown in figure 3.8b when AN13 thresholds is removed. Table 3.4 shows individual thresholds measured behaviorally and objectively.
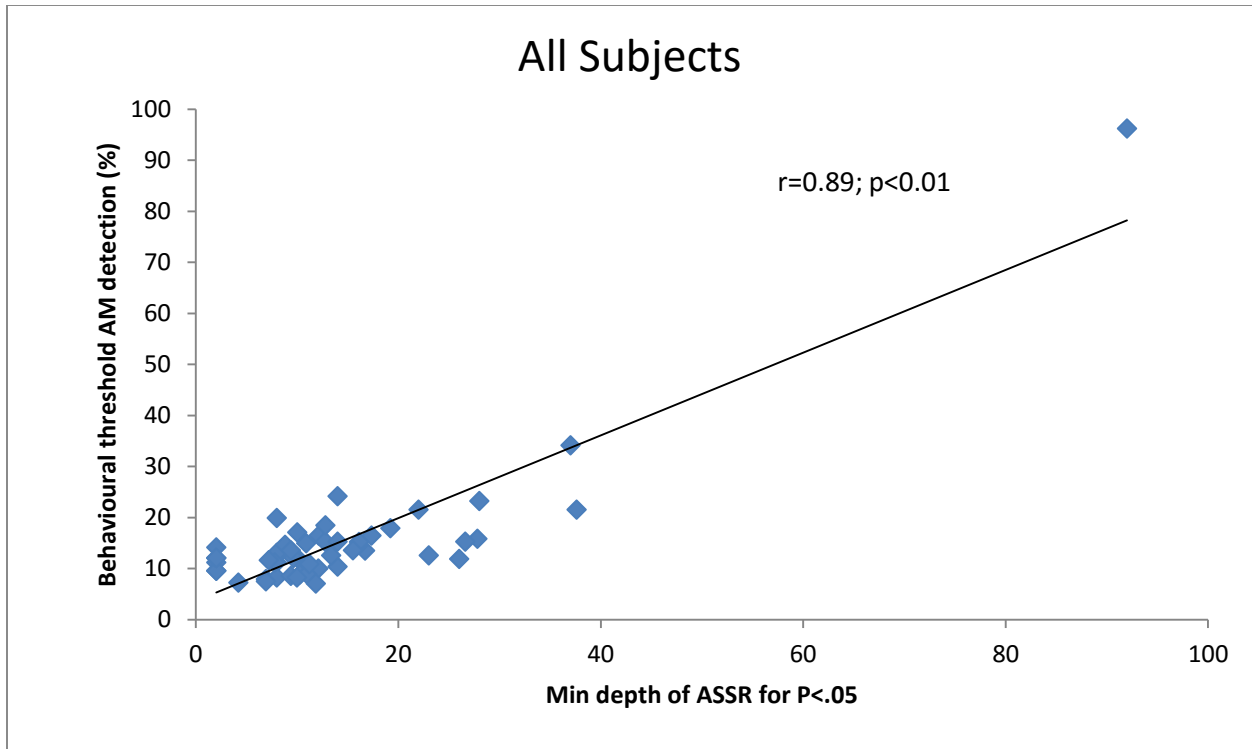
Figure 3. 8a Correlation between behavioral & EFR Thresholds for all subjects
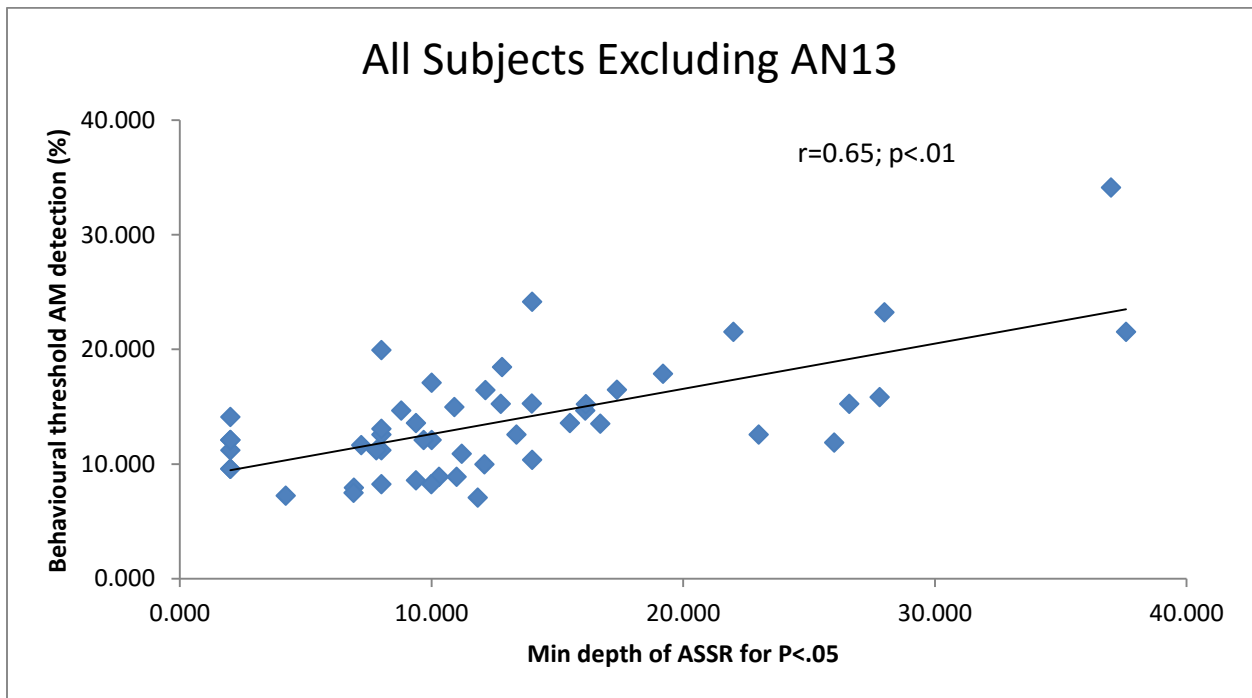
Figure 3. 9b Correlation between Subjective and Objective Thresholds for all subjects excluding AN13.

Table 3. 4 Average and Difference between AM behavioral and EFR thresholds

AN code	Subjective Threshold in dB	Objective-Threshold (EFR p<0.05)	Threshold-Difference
AN27	-9.333	-8.636	-0.697
AN42-RE	-14.943	-14.334	-0.609
AN33-LE	-17.333	-20.562	3.229
AN41-LE	-13.331	-13.152	-0.180
AN32-RE	-16.306	-17.089	0.783
AN41-RE	-12.333	-17.077	4.744
AN32-LE	-17.330	-6.577	-10.753
AN33-RE	-18.667	-22.853	4.186
AN13	-0.333	-0.724	0.391
AN42-LE	-18.500	-11.701	-6.799
AN7-RE	-13.330	-8.496	-4.834
Acoustic Neuroma	-12.667	-12.667	-11.502
The sum of Diff.			-12.149

Comparing AN subjects with normal hearing and other controls, figure 3.9 shows that AN EFR responses required higher AM depth to become significantly above noise-floor.
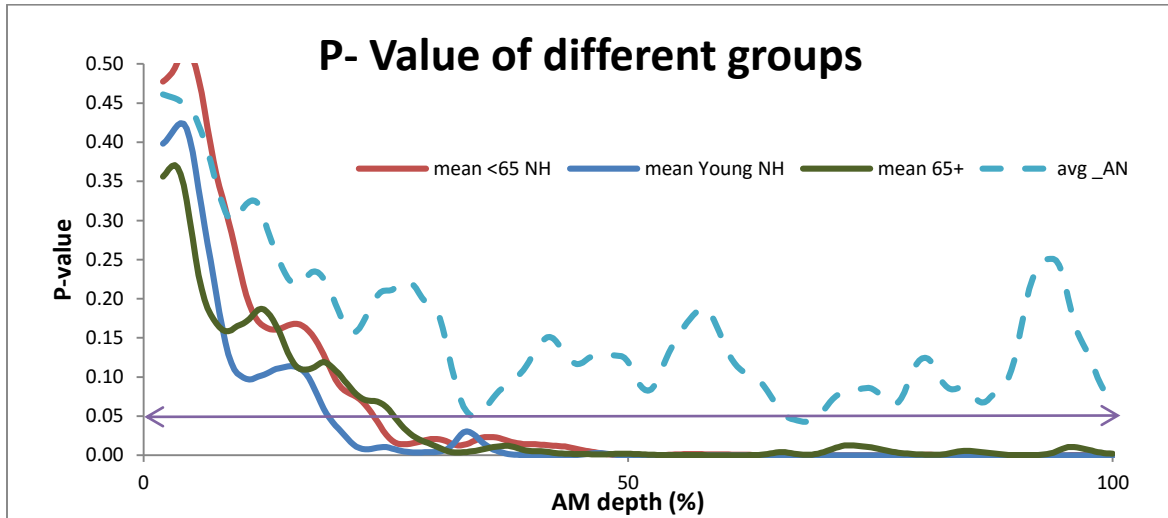
Figure 3. 10 P- Value as a function of AM depth (%) in different groups

Figure 3.10 shows individual EFRs for all AN subjects. Although most adult AN subjects showed a general pattern that was similar to that reported in our previous study (chapter 2), some showed different patterns. For example, both children (AN41, AN42) as well as an adult (AN13) demonstrated a fluctuating pattern.

EFR profiles for AN subjects
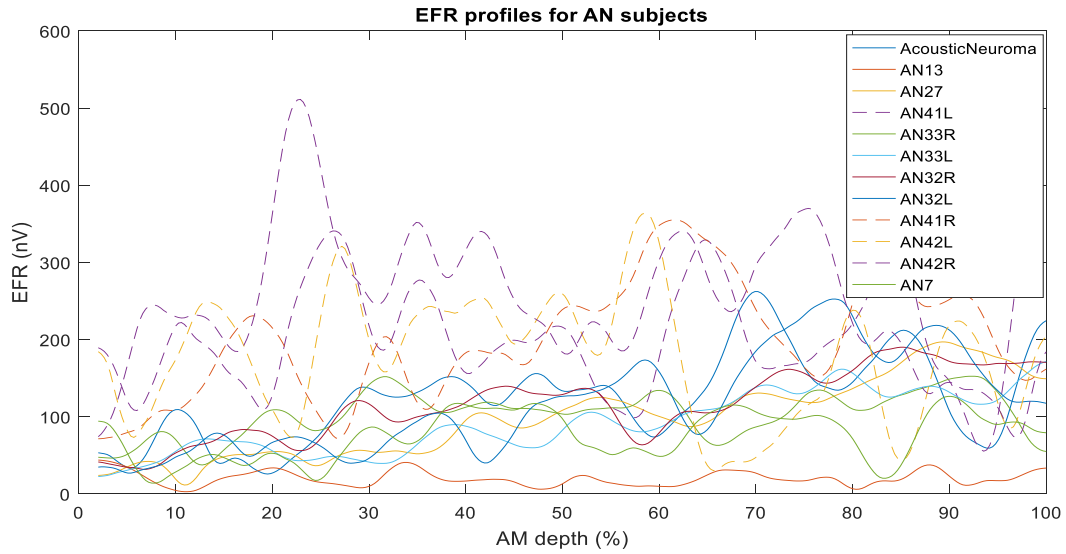
Figure 3. 11 EFR profiles for AN subjects, AN children in dots lines, AN adults in solid lines.

Figure 3.11 shows individual EFRs and their fitted sigmoidal functions. As a comparison, Figure 3.12 replots the same data from a group of young normal-hearing (YNH) subjects reported in a previous study (Dimitrijevic et al., 2016).
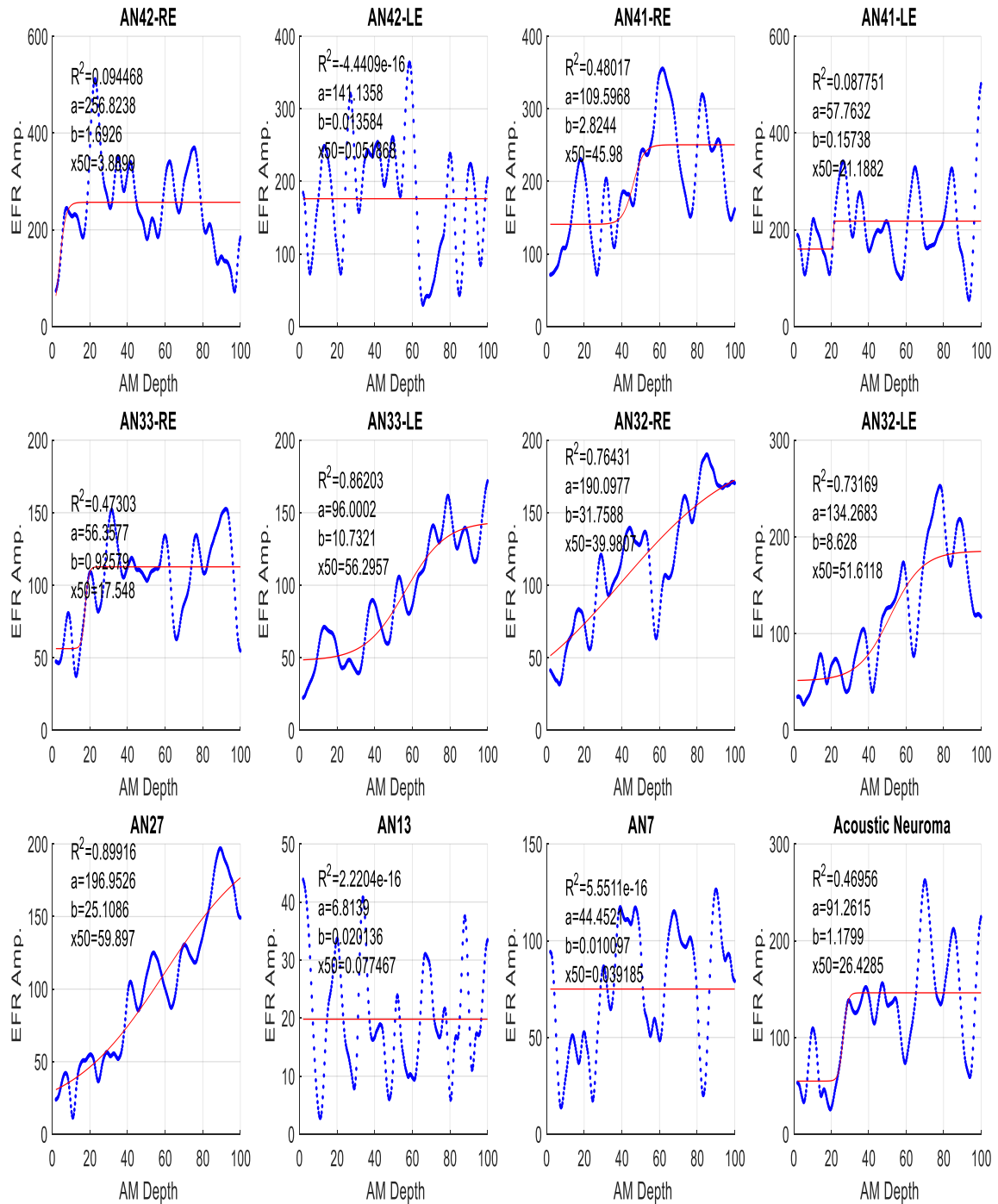
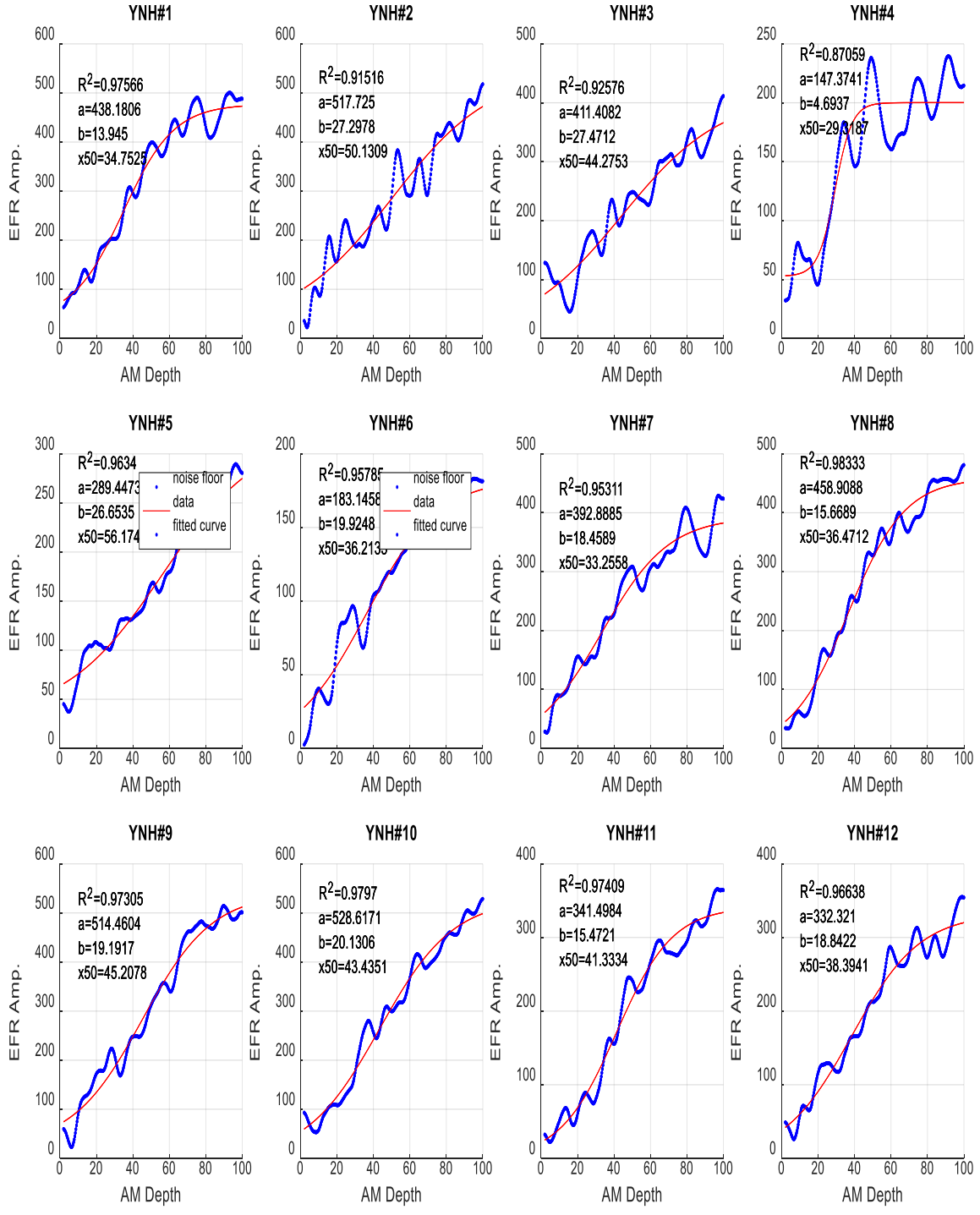**Figure 3. 12 EFR profiles (blue lines) for AN subjects fitted with a sigmoid function (red lines)**

60

Figure 3. 13 EFR profiles for YNH subjects fitted with sigmoid function

Figure 3.13 compares the peak (A) and slope (B) measures between AN and YNH. One-way ANOVA showed a significant difference in both values between the AN and YNH groups.
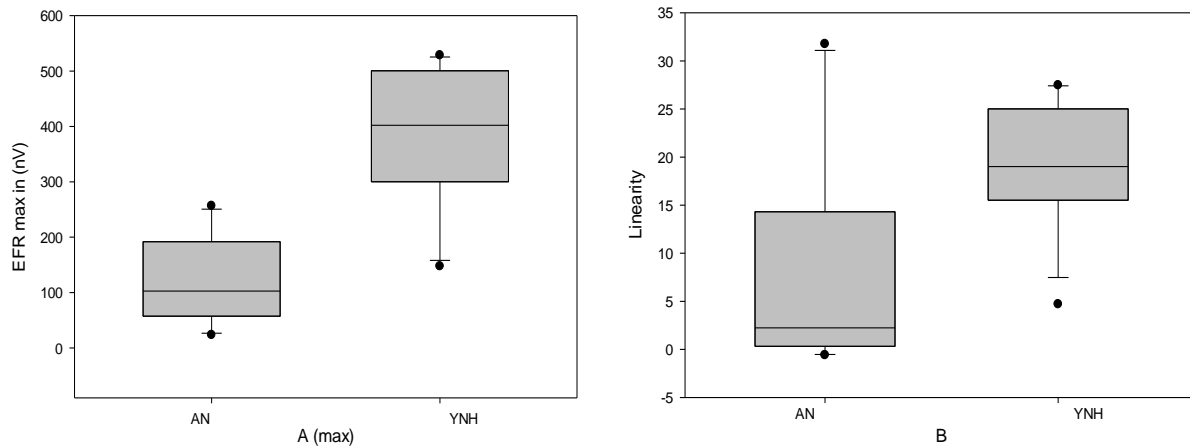

Figure 3. 14 Significant difference is found between AN and YNH groups in terms of A(max), and B (linearity) values

Focusing on children subjects, Figure 3.14 compares the EFR between the child with AN (two ears) and his normal hearing twin (one ear). Different from the monotonically increasing EFR in the normal control, the AN child showed a fluctuating EFR in both ears.
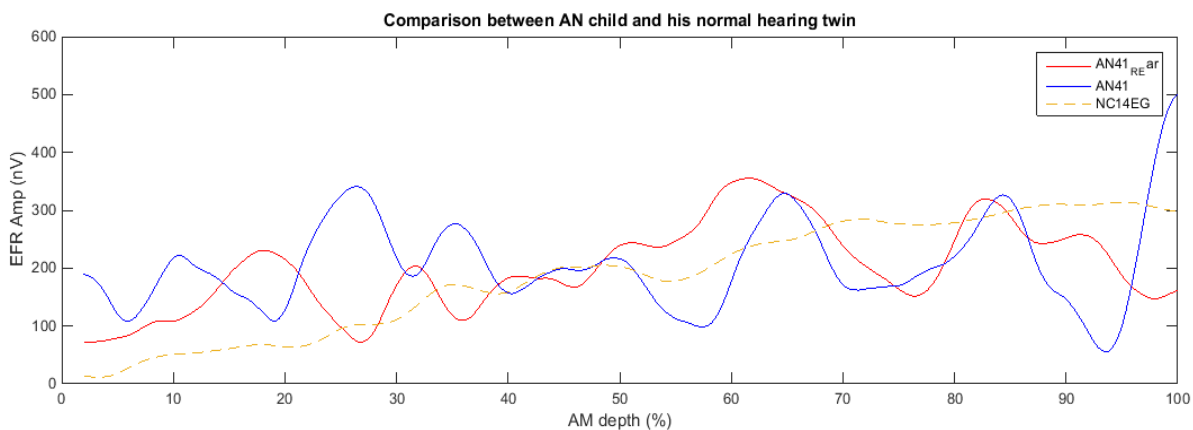

Figure 3. 15 Comparison between twin (dashed line=normal child Vs. solid line=AN child)

Figure 3.15 shows the average over four AN ears (2 per AN child) and two control ears (1 per child).
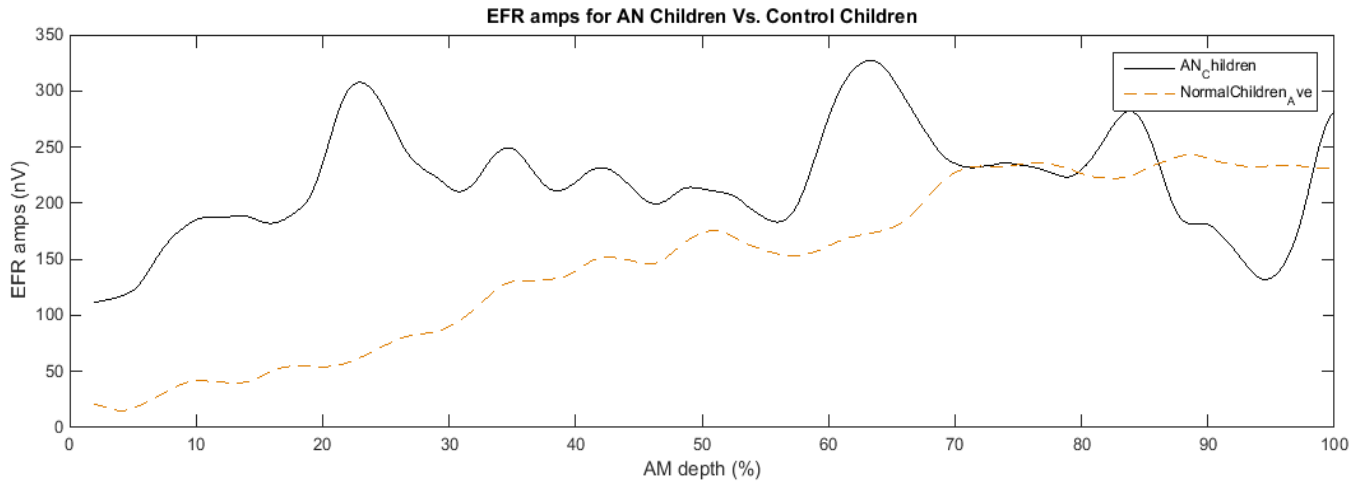

Figure 3. 16 Comparison between the AN children (solid line) Vs. Control children EFR (dashed line)

Figure 3.16 shows AN13's EFR profile which could not be fitted by a sigmoid function. In fact, this what we expected since the modulation frequency is beyond her AM detection threshold that was measured objectively (TMTF).
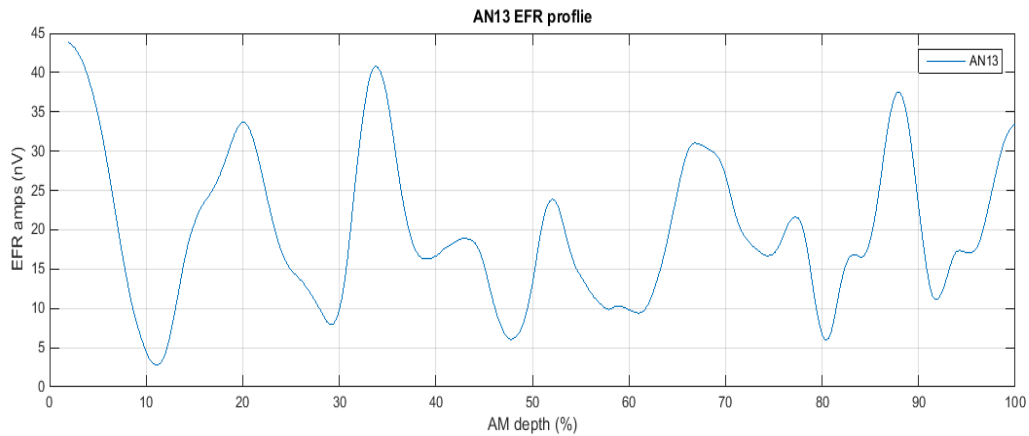

Figure 3. 17 AN13 EFR profile

63

Figure 3.17 compares the EFR from 4 groups, including the AN adult subjects (except for AN13; blue dashed line), the AN children (red dotted line), the young normal hearing control (solid blue line), and the normal-hearing child control (solid cyan line). In addition to the apparent different patterns for the AN subjects, the present result showed smaller EFR in normal children than the young normal adults group described in chapter 2.
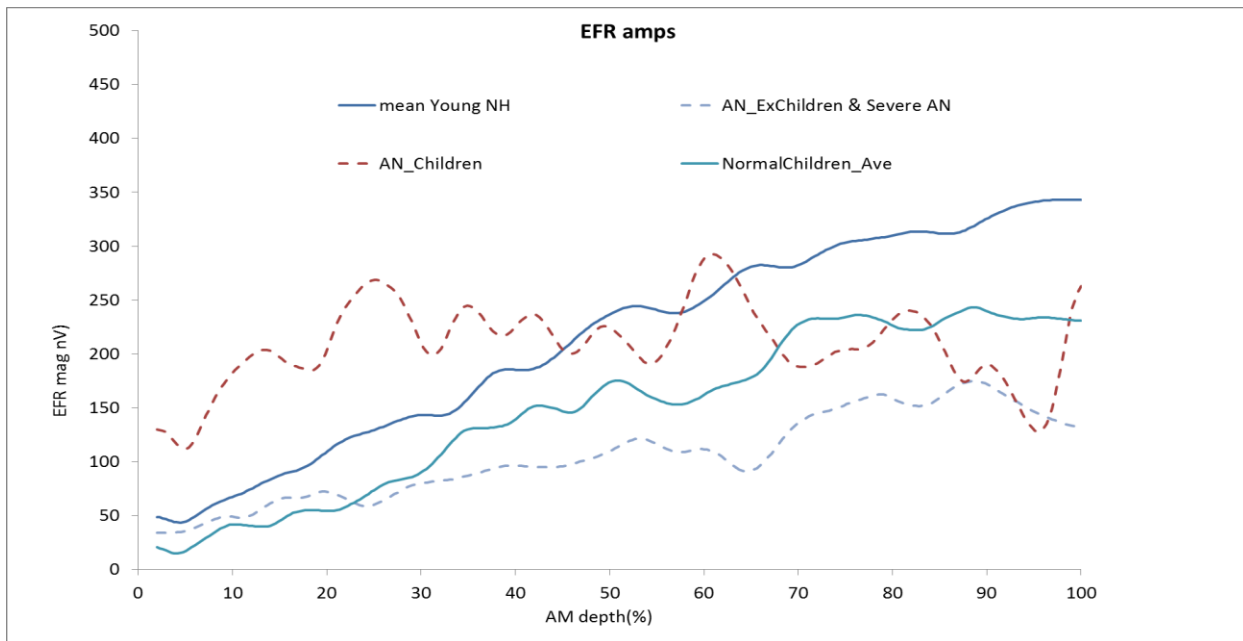

Figure 3. 18 EFR profiles for different groups and sub groups

We followed one normal hearing adult from 21 to 23 years old. Figure 3.18 shows that this subject's EFR tended to increase with age.
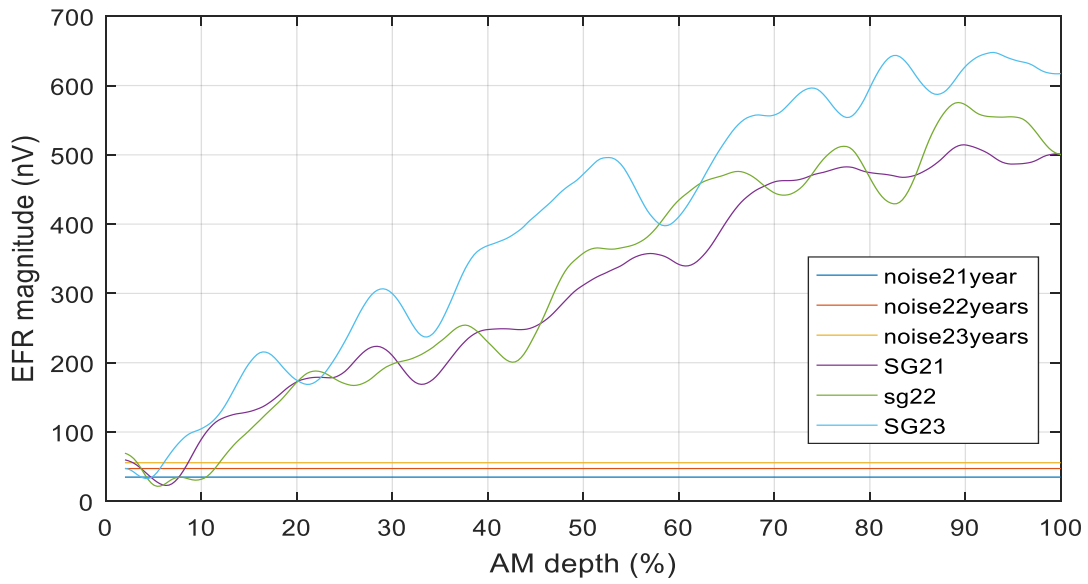
Figure 3. 19 EFR profile for normal subject in different age

In the swept-FM condition, we evaluated the EFR profiles in response to an AM stimulus with modulation rate being varied from 2 to 59 Hz. Figure 3.19 shows that the AN subjects produced significantly smaller EFR than the normal control.
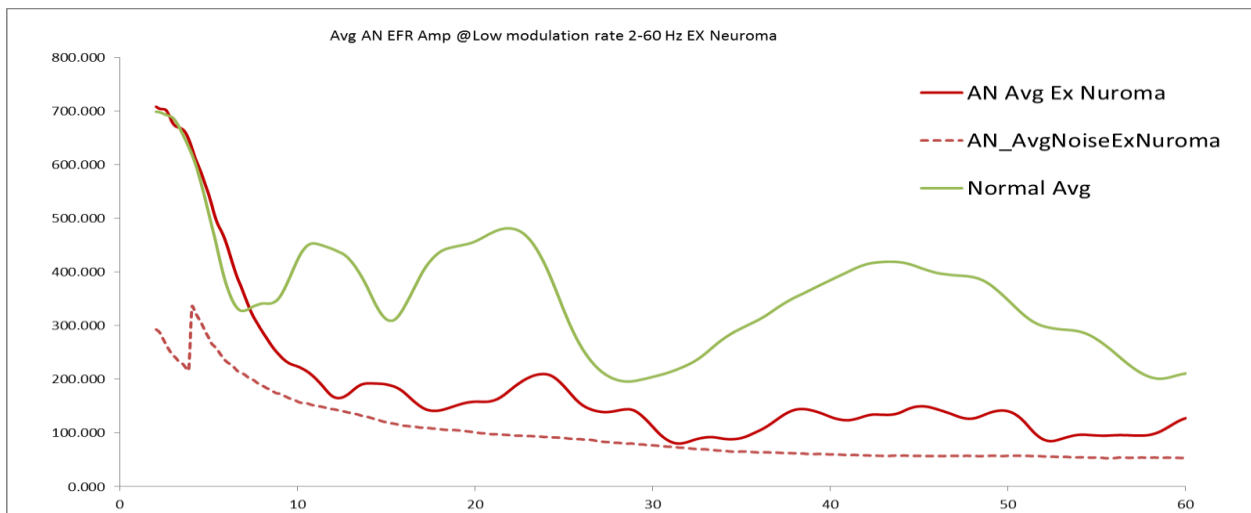

Figure 3. 20 Grand Average of AN profile vs. Normal subject for the low modulation rate

Figure 3.20 shows individuals EFR responses at low modulation frequencies for all AN subjects.

EFR Amp @Low modulation rate 2-59 Hz
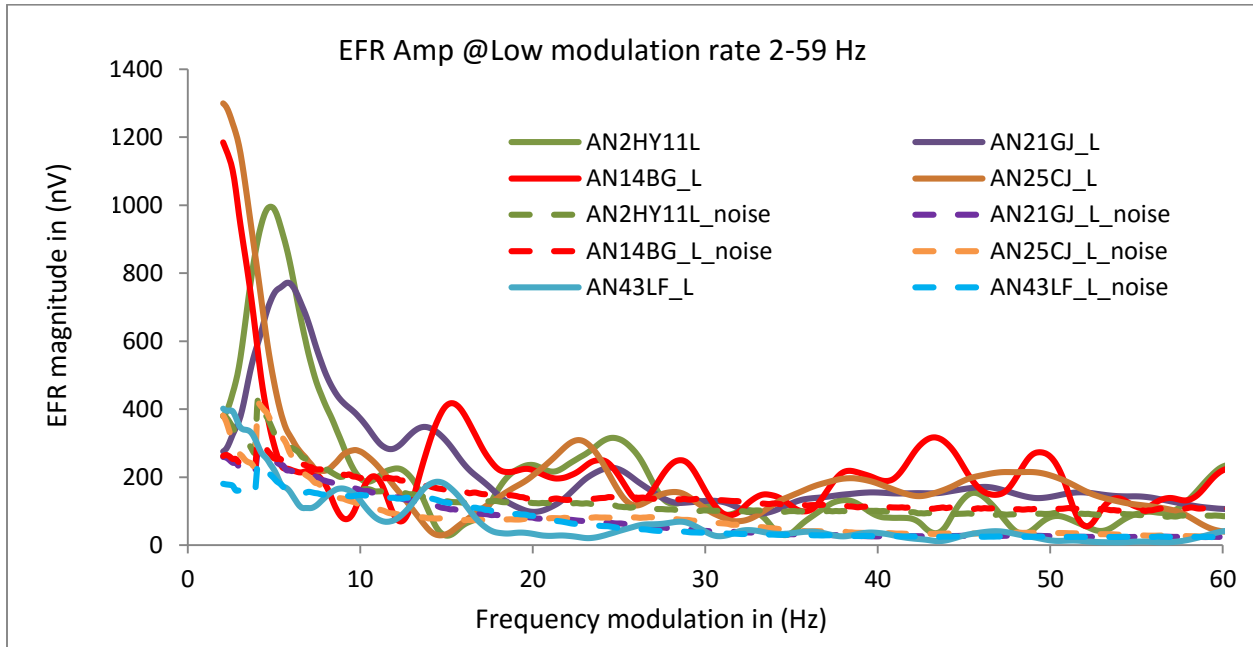
Figure 3. 21 EFR modulation rate 2-59 Hz, solid line referred to the response and dashed line refer to the noise floor.

In the 2nd session of the swept-FM condition, we evaluated the EFR profile throughout relatively higher modulation frequencies from 62 to 300 Hz. Figure 3.21 shows not only significantly smaller than normal EFR in AN subjects but also significantly lower than normal cutoff frequency (120 vs. >300 Hz) at which the reliable EFR could be measured.

Figure 3. 22 EFR of Normal Vs. AN
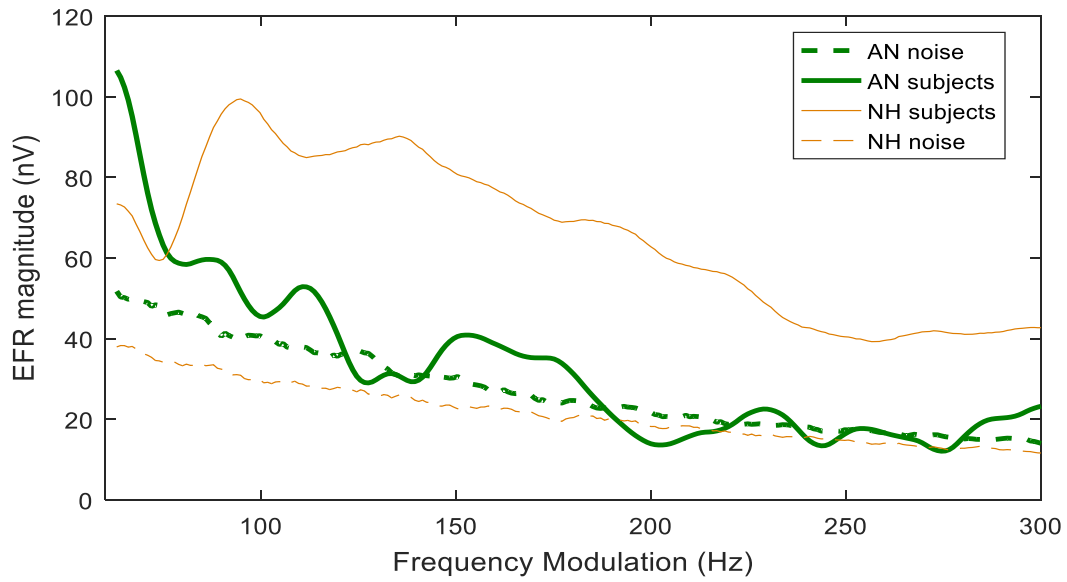
Figure 3.22 shows a discrepancy between the EFR and behavioral TMTF in AN13. Although this subject lacked significant EFR at most modulation frequencies, she was able to detect modulation at frequencies up to 40 Hz.
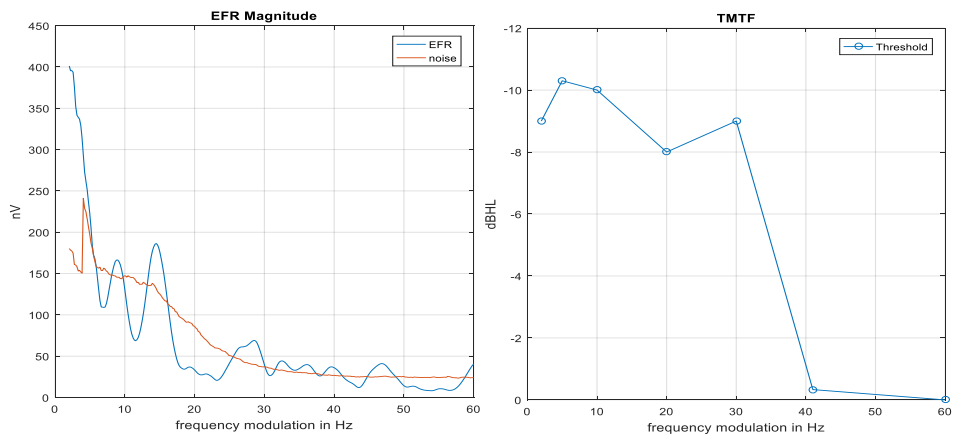

Figure 3. 23 Comparison between objective EFR (A-left panel) and Behavioral TMTF (B-right panel)

Discussion

The present study confirmed previous behavioral findings that the AN subjects have a significantly elevated amplitude modulation detection threshold compared to normal subjects. The present study also introduced a novel electrophysiological method to objectively assess temporal acuity. The present result showed a significant correlation in modulation detection between behavioral and electrophysiological measures. This significant correlation has important clinical implications, specifically for measuring temporal acuity in infants and special populations such as those with a cognitive disability, whose behavioral thresholds cannot be reliably measured.

The present study contained several limitations. First, the sample size was small. Second, the EFR results did not reveal any consistent EFR patterns in AN subjects who may have different etiologies, e.g., presynaptic or postsynaptic mechanisms. Third, the present results suggested a development component in the EFR, but the small sample size limits its interpretation.

CHAPTER 4

Summary and Conclusions

The overall purpose of this dissertation is to evaluate the effectiveness and suitability of using the "sweep" stimuli (e.g. varying the AM depth or the FM rate) to elicit envelope following responses. The first aim is to measure and correlate between the EFR-AM and behaviorally measured modulation thresholds in normal-hearing subjects, including young and elderly listeners. The second goal is to extend these measures and analytic tools to the auditory neuropathy population. Significant correlation was found between our proposed objective and subjective method. Thus, clinicians and audiologists should consider our method a reliable diagnostic tool to evaluate objectively temporal acuity. This tool would be especially useful in special populations such as infants with auditory neuropathy or patients with limited cognitive or mobile abilities. Additionally, the present study discusses the possibility of relating the characteristics of the EFR-modulation transfer function (MTF) profiles to known sites of the lesion in individual AN subjects to help identify the underlying mechanisms. Finally, the present study will have a significant impact on the treatment of auditory neuropathy because it will allow clinicians to measure the degree of the AN severity even when the child or individual is unable to provide informative responses about the way they hear. This will help the ENT surgeons to determine whether the AN patient is a good candidate for a cochlear implant or not.

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