PERIODICITY ENVELOPE ENCODING: EVIDENCE FOR TWO SITES OF
INTRODUCTION

by

Allison Bailie MacEacheron

Submitted in partial fulfillment of the requirements
for the degree of Master of Science

at

Dalhousie University
Halifax, Nova Scotia
March 2015

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

The Envelope Following Response (EFR) has been under investigation as part of the ASSR evoked potential but it is unclear where exactly this periodicity envelope originates. The commonly accepted theory holds that the periodicity envelope is introduced due to cochlear interactions and non-linearities but this does not account for measurable EFR responses to resolved stimuli (i.e. stimuli that should not interact on the basilar membrane; Korczak *et al.* 2012). Laroche *et al.* (2013) therefore proposed that the EFR to resolved stimuli arises centrally. To investigate this theory, EFR were measured to stimuli of different modulation rates, component frequencies, and phase relationships in normal hearing individuals. When stimuli were unresolved, response amplitude was seen to increase with decreasing degree of resolution and decrease when the envelope was minimized in the stimulus via phase manipulation, supporting the accepted hypothesis. When stimuli were resolved, response amplitude decreased with increasing component frequency (suggesting that phase locking is required) and responses were unaffected by phase-based minimization of the stimulus envelope. This evidence supports the theory that EFR to resolved harmonics is introduced centrally for it suggests that temporal encoding of the stimulus components by auditory nerve fibers is required before an EFR can be reliably measured. We therefore conclude that the periodicity envelope measured in the EFR is introduced at different levels along the auditory system depending on the resolution of its components.

LIST OF ABBREVIATIONS USED

ABR	Auditory Brainstem Response
AM	Amplitude modulation
ANOVA	Analysis of variance
ASSR	Auditory Steady State Response
CB	Critical band
CF	Characteristic frequency
EFR	Envelope following response
f_0	Fundamental frequency
FFR	Frequency following response
FM	Frequency modulation
IC	Inferior colliculus
ITD	Interaural timing difference
MGB	Medial geniculate body
PTC	Psychophysical tuning curve
R	Vector strength
rBMF	Best modulation frequency- rate
Rmax	Synchronization index
SAM	Sinusoidally amplitude modulated
SNR	Signal to noise ratio
SOC	Superior olivary complex
SPL	Sound pressure level
SR	Spontaneous rate
tBMF	Best modulation frequency-rate
TFS	Temporal fine structure

CHAPTER 1   INTRODUCTION

A speech signal can be broken up into two temporal components: the temporal fine structure (TFS) which consists of the individual frequency components of speech, and the spectro-temporal speech envelope associated with the movements of the articulators that rise and fall with each speech sound. A third temporal component is sometimes distinguished as well, called periodicity, which is thought to arise when TFS components interact in the auditory system to introduce energy that is not present in the stimulus (Rosen, 1992). The *periodicity envelope* is an amplitude modulated (AM) signal (Picton, 2013) and one of the foci of this study. Temporal fine structure (and perhaps the periodicity envelope) provides the brain access to interaural latency differences for sound localization, and allows the brain to distinguish between speech and background noise (Langner, 1992).

In light of the potential importance of the periodicity envelope for speech understanding this study will focus on where along the auditory pathway this envelope is introduced. Neurons in the peripheral and central nervous system synchronize their responses to temporal fine-structure and to the periodicity envelope, and this synchronized activity can be measured as electric potentials at the scalp (Korczak, Smart, Delgado, Strobel, & Bradford, 2012). We will therefore measure the electrophysiological response to sustained amplitude modulated tones (i.e. the Envelope Following Response or EFR, also known as the Auditory Steady State Response or ASSR), investigating how responses change with frequency, resolution of the components, and phase manipulations. The trends found in this data will be considered in light of the known properties of the auditory system to investigate whether the periodicity envelope arises solely in the periphery (as is commonly thought) or whether there is a central component (Laroche, Dajani, Prévost, & Marcoux, 2013). Before going into the detail of the present study we will discuss the basic processes whereby AM signals are extracted from spectral frequency information, encoded and processed along the auditory pathways.

1.1 Complex Signals

Complex signals, such as speech, differ from simple pure tones in that they are composed of numerous spectral frequency components that vary over time. As a complex waveform enters the cochlea it is decomposed along the basilar membrane with each frequency component causing maximum displacement at a region corresponding to its characteristic frequency (Gelfand, 2010). The picture is complicated, however, when the component frequencies are close enough to each other to stimulate similar regions on the basilar membrane, causing overlapping displacement patterns and giving rise to energy at frequencies not present in the stimulus. One of the most prominent frequencies introduced, occurring at the difference frequency, is known as the periodicity envelope (also known as the fundamental frequency (f_0) in the pitch literature (Khanna, 2002)).

Amplitude modulated tones, or AM tones, are a common type of complex tone found in speech and most natural sounds. One commonly occurring form of perceptible amplitude modulation is the beat, which is created when two similar component frequencies are played simultaneously. For example, when two sine waves of similar frequency enter the cochlea, say 1020 and 1023 Hz, their excitation patterns overlap a great deal on the basilar membrane. These two out-of-phase sine waves give rise to neural responses that are phase-locked to their frequencies as well as temporal firing patterns related to the difference between the tones, called the periodicity envelope (Hartmann, 1997). This leads to a percept of the average frequency of the two tones with a cyclically rising and falling amplitude that corresponds to the difference between the two frequencies (1021.5 Hz tone beating at 3 Hz in this example). Called a 'beat', this interaction of signal components has been studied to give more insight into wave interaction in the cochlea (Hartmann, 1997). Another form of AM is a sinusoidally amplitude modulated (SAM) tone consisting of three stimulus component frequencies. One way to create sinusoidally amplitude modulated tones in the laboratory is to present three component tones: one, called the 'carrier frequency', with two equally spaced 'side-bands' on either side that are half the amplitude of the carrier. The modulation frequency is the difference between the carrier and one of its sidebands (f_2-f_1), just as it is with

2

beats. For example, three component tones of 934 Hz, 1008 Hz, and 1082 Hz would create an 1008 Hz tone amplitude modulated at 74 Hz (1082-1008= 74 Hz) (Picton, John, Dimitrijevic, & Purcell, 2003a). Constructive and destructive interference between signal components creates a signal that waxes and wanes periodically with a sinusoidally shaped envelope.

1.2   Amplitude modulation encoding throughout the auditory system

1.2.1   Introduction of amplitude modulation- the cochlea

As a speech signal enters the cochlea it is decomposed into its spectral frequencies along the basilar membrane. This spectral information is encoded faithfully by phase locking to the stimulus components as well as place code. When the mechanical vibrations of the basilar membrane are measured, however, there is energy present at additional frequencies not present in the input, including the frequency of the difference between spectral components (Khanna, 2002). McFadden (1988) investigated this phenomenon and found that this difference frequency is detected perceptually even when masking noise is presented around the difference frequency's CF. Somehow, therefore, energy at the difference frequency (periodicity envelope) is being introduced in regions of the basilar membrane not tuned to the difference frequency.

When two sine waves of equal amplitude but slightly different frequency are introduced into the cochlea constructive and destructive interference on the basilar membrane occurs, introducing non-linearity (Khanna, 2002). These are called unresolved tones. The spectral fine structure of the original stimulus is still present in the signal and basilar membrane movement, so cochlear transduction causes phase locking and neurotransmitter release at regular intervals locked to the tones (Lins, Picton, & Picton, 1995). What has changed, however, is the amplitude of each waveform peak. Where constructive interference occurs the amplitude of the waveform is double the original, and the resultant basilar membrane movement creates a stronger neurotransmitter release than for regions of destructive interference (Burkard, Eggermont, & Don, 2007). This change in the amplitude of the signal is encoded as additional information along with the

carrier frequency—introducing AM information to the auditory system. The same principle applies to interactions between the components of a harmonic signal. The equal spacing of the harmonic components introduces modulations at the fundamental frequency into the auditory pathway (Aiken & Picton, 2008).

1.3   The auditory nerve

Faithful transmission of the periodicity envelope is clear in the auditory nerve. Peri-stimulus time histograms from the auditory nerve show highest and lowest responses corresponding temporally to the regions of constructive and destructive interference of the stimulus, respectively (Joris, Schreiner, & Rees, 2004). Just as phase locking is known to occur to the fine structure, phase locking occurs to the envelope if at least two stimulus frequency components fall within the inner hair cell's tuning curve (Javel, 1980).

Auditory nerve fibers have different spontaneous firing rates (SR) and different degrees of phase locking synchronization with the incoming stimulus. Designated R or 'vector strength', this index of synchronization is calculated using the amplitude and phase of individual neural spikes using the following equation:

$$R= \sqrt{(\Sigma \cos\theta)^2 + (\Sigma \sin\theta)^2}/n$$
$$\text{Where: } \theta=\arctan (\Sigma y_i/\Sigma x_i) + k\pi,$$
$$n= \text{number of vectors}$$

with values 0–1, 1 being perfect synchronization (Goldberg & Brown, 1969). Studies done by Joris and Yin (1992) and Wang and Sachs (1993) found that low and medium SR neurons have better phase locking synchronization (R values or f_0 synchronization index), than high SR neurons. This trend is only seen, however, when the high SR fibers are presented with quiet stimuli and the low SR fibers are presented with loud stimuli as these are the stimulus levels where each type of neuron optimally responds. Based on this information it is logical to conclude that mid to high-level SPL stimuli are optimally

4

encoded by low and medium SR fibers of the auditory nerve—precisely the conditions of most speech stimuli (Joris *et al.* 2004).

It was suggested by Laroche *et al.* (2013) that energy at the periodicity envelope may not arise exclusively due to cochlear non-linearities but may also be introduced in a brainstem nucleus by central interactions between component responses. For interactions to occur between responses to individual components these components must first be encoded in the auditory nerve; that is to say that phase locking to the spectral components is necessary for central interaction. Most estimates place the phase locking limit of the auditory nerve at 4–5 KHz in humans and animals (Rose, Brugge, Anderson, & Hind, 1967). We would therefore not expect periodicity envelope energy to arise due to central interaction if the component frequencies were beyond the phase locking limits of the auditory nerve. This hypothesis will be investigated further in this study.

1.3.1 The cochlear nucleus

Divided into different regions and cell types, the cochlear nucleus, like the auditory nerve, faithfully transmits AM information. It differs from the auditory nerve in that it has a wider dynamic range, is less sensitive to background noise, and has higher gains, but modulation encoding remains temporally based (Joris *et al.* 2004). It also has many cell types that have a variety of response patterns, not simply primary-like responses as in the auditory nerve. Various cell types within the cochlear nucleus have different functions and abilities to phase lock to AM envelopes. Most applicable to this discussion are the 'chopper' type cells which fire at regular intervals for the length of the stimulus and 'onset' cells which show very strong and sharp periodic responses. Known as 'modulation detectors' or 'intrinsic oscillators', individual cells of the chopper type have different best modulation frequencies (tBMF), possibly creating a modulation filterbank of sorts (Joris *et al. 2004*). It has been proposed that these cells with different tBMF act to decompose the envelope spectrum in a similar way to the filtering of spectral frequencies to different cell regions of the cochlear nucleus. Kim, Sirianni and Chang (1990) found a correlation (r=0.86) between the intrinsic oscillation of individual CN neural responses and BMF in the decerebrate cat to support this hypothesis. Another cell

type that shows good synchronization indices (Rmax) to the modulation envelope are primary-like cells. This type of neuron fires most strongly at the onset of a stimulus and has even better gain values (similar to Rmax) than their other primary-like counterpart: the auditory nerve (Frisina, Smith, & Chamberlain, 1985 & 1990). When chopper and primary-like neurons are compared, better gains are found in chopper cells when the modulation rate is < 500 Hz. At higher modulation rates the reverse is true (Rhode & Greenberg, 1994). The onset cell type, however, has the strongest periodicity envelope phase locking and the widest response field of any cell type in the cochlear nucleus. Many auditory nerve fibers converge on these cells, allowing for a strong response to nearly every period of the input when the modulation frequency is sufficiently low (Langner, 1992). In addition to this enhancement of temporal regularity present in the auditory nerve fibers, these cells can also produce temporal responses at additional frequencies (Joris *et al.* 2004).

1.3.2   *The superior olivary complex*

The superior olivary complex (SOC) plays an important role in AM processing because it is where the temporally-based code begins to be converted to a rate based code (Joris *et al.* 2004). Up until this point in the auditory pathway, we have been most concerned about the synchronization of neural firing to the stimulus or temporal code. While this is an optimal method for transmitting envelope information in the periphery, the limits of phase locking become lower and lower with each integrative stage along the auditory neuroaxis, and a temporal code would greatly limit the transmission of AM envelope information to the auditory cortex (Langner & Schreiner, 1988). Rate based code, however, does not require phase locking synchronization. Temporal to rate conversion minimizes the limitations of phase locking and acts as the first true neural processing of the AM envelope information.

While very little is known about the conversion mechanism of a temporal to a rate-based code, large differences in the numbers of neurons that respond optimally to rate (rBMF) versus temporal (tBMF) information in the cochlear nucleus in comparison to the inferior colliculus suggest that some of this change could be occurring in the SOC,

but that the IC is also responsible (Joris *et al.* 2004). Langner and Schreiner (1988) found that 75% of single unit neurons in the IC of the anaesthetized cat were tuned to rBMF, versus 33% that were tuned to tBMF, while rBMF neurons are not commonly found in the cochlear nucleus (Frisina *et al.* 1990; Kim *et al.* 1990). Since not all auditory pathways travel through the SOC, it is very likely that some temporal to rate coding begins in the SOC and is furthered in the inferior colliculus while the majority occurs in the IC itself.

Modulation detection and interaural comparison in the SOC is thought to be responsible for sound localization at low frequencies. The temporal precision required for interaural envelope comparison is very exact—down to microseconds (Henning, 1974). Humans have a remarkable ability to detect the slight timing differences of modulations arriving at both ears (ITD), indicating that very accurate envelope information is reaching the SOC and that interaural interaction is occurring at this site. One example of this interaural interaction is binaural beats wherein signals close in frequency are encoded in each ear and their interaction in the SOC causes the subject to perceive amplitude fluctuations, or beats (this phenomenon does not occur in general speech encoding; Perrot & Nelson, 1969). From this we can conclude that the SOC maintains accurate temporal information despite its partial conversion to rate code.

1.3.3   The inferior colliculus

As the primary processing centre and mandatory midbrain nucleus for most auditory information, the inferior colliculus also plays an important role in AM processing. Although some of the envelope information appears to be converted to a rate code in the SOC, the large majority is believed to be converted in the IC. Neurons temporally locked to the stimulus are still present in the IC, however (Joris *et al.* 2004). Hewitt and Meddis (1994) proposed a computer model for temporal to rate-based coding in the inferior colliculus. They suggest that one inferior colliculus cell receives temporal information from several cochlear nucleus neurons, only firing when it receives many synchronous inputs, to create a rate-based code. It can be noted that this model does not take the SOC into consideration in its modeling parameters. Rees and Møller (1987)

7

found that the IC tBMF of the rat ranged from 100–120 Hz while similar phase locking limits were found in the squirrel monkey and gerbil (Reese & Palmer, 1989, Krishna & Semple, 2000). These low phase locking limits correspond with the previously discussed phenomenon of progressively lower limits further along the auditory neuroaxis. In contrast, IC neurons exist with rate BMF (rBMF) as high as 1000 Hz in the cat and 800 Hz in the bat (Langner & Schreiner, 1988; Cordon, White, & Feng, 1996). This alone shows the benefit of rate encoding of envelope information for, without it, only very low frequency envelope information would be carried to the auditory cortex. The purpose of the dual envelope encoding mechanisms is unclear (both rBMF and tBMF) but it has been suggested that the envelope information gleaned from each provides different functional value (Joris *et al.* 2004).

Further evidence to support the idea that AM information is carried through modulation filterbanks was found in the IC of the cat by Schreiner and Langner (1988). They were able to map the rBMF of IC neurons and found that BMF extends along the dorsal-ventral axis with higher rBMFs being found deeper in the IC structures. The authors termed the rBMF organization as 'quasi-concentric' with the highest BMF in the lateral 1/3 and progressively lower BMF further away from this highest BMF point. The isocontours are cone-like in shape and orthogonal to the spectral frequency map. Though the neural organization does have some discontinuities, it demonstrates a structural basis for envelope encoding.

1.3.4   The thalamus

Though the medial geniculate body (MGB) of the thalamus is the last major relay station before the auditory cortex, little is known about its AM encoding abilities or how they differ from that of the inferior colliculus (Joris *et al.* 2004). One study on squirrel monkeys suggests that thalamic tBMF are bandpass and are able to phase-lock to modulations of 2–128 Hz (Preuss and Müller-Preuss, 1990), while another study found the limit of phase locking to be 200 Hz (Rouiller, De Ribaupierre, Toros-Morel, & De Ribeaupierre, 1981). It is interesting to note that no difference was found between rBMFs

and tBMFs in the MGB, suggesting that at low frequencies most of the AM information is carried temporally rather than by firing rate (Preuss and Müller-Preuss, 1990).

1.4   ASSR and modulation encoding

The Auditory Steady State Response (ASSR) is a scalp-measured electrophysiological potential that follows the stimulus for its duration with a constant phase and amplitude. This response follows amplitude or frequency of modulation (AM or FM) in the stimulus, allowing researchers and clinicians to investigate the integrity of temporal encoding in the auditory system (Picton *et al.* 2003). Unlike the commonly used ABR, the ASSR is generally analyzed in terms of phase and frequency instead of latency. For this reason ASSR measurements are usually converted using Fourier transforms or similar procedures (e.g., autocorrelation) into the frequency domain. They can be analyzed by statistical means for presence or absence of the response, making the ASSR a truly objective measure (Korczak *et al.* 2002). When analyzing the frequency plot of a response, a number of peaks will be seen: a response to the modulation frequency and a response to the signal components if they are within the range of phase locking in the auditory nerve (Lins *et al.* 1995, Rose *et al.* 1967). The response to the modulation is called the ASSR or the Envelope Following Response (EFR) because it represents the encoding of the periodicity envelope of the signal whereas responses to the individual components can be called the Frequency Following Response (FFR; Laroche *et al.* 2013). The term FFR is often used more generally to refer to both frequency and envelope components. In the present paper, this more general usage will be avoided for the sake of clarity.

The ASSR has many potential clinical uses including hearing threshold estimation, evaluating temporal and frequency encoding at a suprathreshold level, and monitoring anesthesia levels during surgery (Picton *et al.* 2003b). Its most prevalent use today is in hearing threshold estimation in infants, young children, and those with cognitive, social, and emotional problems that do not allow for reliable behavioral testing. With a set-up similar to an ABR, the ASSR can be measured at four audiometric frequencies (500, 1000, 20000, 4000 Hz) in both ears simultaneously, reducing testing

9

time (Picton, Dimitrijevic, & John, 2002; Korczak *et al.* 2002). The ASSR can also be done on calm but awake patients, eliminating the need for sedation in the pediatric population, although higher modulation frequencies are ideal for testing sleeping individuals (Rance & Rickards, 2002). The ASSR has not demonstrated practical use for threshold estimation in patients with auditory neuropathy and neurologic disorders such as brainstem and thalamic lesions (Harada, Aoyagi, Suzuki, Kiren, & Koike, 1994).

1.5   Source and generation of the ASSR

The neurophysiologic source of the ASSR has been under investigation for many years in hopes to broaden our understanding of temporal processing in the auditory system (Picton *et al.* 2003a; Lins *et al.*, 1995). The source of an electrophysiological response can be defined as the neurological region that creates the measured dipole and interestingly, it has been seen to change in the ASSR with modulation rate, as would be predicted on the basis of the shift from temporal to rate encoding as the neuroaxis is ascended (Lins *et al.* 1995). Using Brain Electric Source Analysis, Herdman and colleagues (2002) showed that 80 Hz ASSRs were primarily of brainstem origin while 40 Hz ASSRs were primarily of cortical origin (supratemporal gyrus), though a smaller brainstem component continues to exist (relative to cortical component). This data was further corroborated by magnetoencephalographic studies showing a longer latency for the 40 Hz ASSR (Herdman *et al.* 2002; Hari, Hamalainen, & Joutsiniemi, 1989).

The dipole source(s) of the ASSR do not need to be identical to the neural mechanisms that are responsible for their introduction. For instance, the ASSR measured from the top of the head may have little contribution from the auditory nerve but the temporal coding in the auditory nerve must play a role in driving the synchronization at the source. For the purposes of this thesis it will be helpful to consider separately where the periodicity envelope information, which is not present in the stimulus, is actually introduced or initiated along the auditory pathway. The accepted theory of ASSR initiation explains that energy at the modulation frequency is introduced along the basilar membrane and at the point of transduction for it is found in the cochlear microphonic and neural response but not in the acoustic signal itself (Nuttall & Dolan, 1996). After

10

undergoing rectification, the ASSR (or EFR) to the modulation component can be seen in the auditory nerve. (Khanna & Teich, 1989; Picton, 2001). Taken together with the known basilar membrane interaction between signal components with beats, it is logical to conclude the ASSR is initiated in the cochlea and propagated through the auditory system. A recent study, however, has provided results that challenge this hypothesis (Laroche *et al*., 2013).

1.6   Resolution and the ASSR

Based on the widely accepted initiation theory, energy at the periodicity envelope of the ASSR is introduced due to cochlear interaction and non-linearities. It would therefore follow that this envelope should only arise when individual components are close together in frequency, where cochlear interaction is possible (Moore, 2008). It has been found, however, that an EFR can be measured to components that are unlikely to interact on the basilar membrane or to stimulate similar peripheral neural fibers (Greenberg, Marsh, Brown, & Smith, 1987). Any interaction between such components would likely have to occur post-synaptically, creating a second site of periodicity envelope initiation that is not included in the current theory. Laroche *et al.* (2013) postulated that there are in fact two sites of EFR initiation, one cochlear and the other at a brainstem locus, that converge on a nucleus in the upper brainstem to create the source we measure in the ASSR. They further suggest that it is the resolvability of the components that determines where along the neuroaxis the majority of the periodicity envelope is introduced. Stimulus components that are close together in frequency, or unresolved, create a periodicity envelope with a cochlear site of introduction while components that are very spread apart on the basilar membrane (resolved) introduce a periodicity envelope in the central nervous system. The studies described in this thesis were designed to test these hypotheses. As an understanding of cochlear resolution is imperative for our hypothesis, a brief detour will be taken to discuss frequency selectivity and critical bands.

The frequency selectivity of the auditory system is determined by how far apart in frequency two signals must be in order to be processed independently (i.e. resolved).

11

Using masking, loudness measures, phase sensitivity etc., researchers have developed the concept of the critical band (CB) to define ranges of frequencies that when played simultaneously create a perceived interaction (Scharf, 1961). The idea of critical bands can be seen in Fletcher's (1940) masking experiments wherein he discovered that as the bandwidth of masking was widened, masked thresholds increased to a certain point which he named the 'critical bandwidth' and then did not increase with further widening. This demonstrates that masking noise and the test tone are similarly encoded over a certain frequency range but not beyond. Scharf (1961) estimated that each critical band is approximately 1-2 mm along the basilar membrane but this is only a rough guideline- critical bands widen with increasing frequency due to the logarithmic basilar membrane spacing of characteristic frequency (Moore & Glasberg, 1983).

This investigation into critical bands gives us valuable insight into the perception of similar tones but not neural encoding mechanisms. Psychophysical tuning curves (PTC; which plot the amount of masking centered around different CF needed to just mask a tone) resemble neuronal tuning curves in their shape but are much wider due to the fact that they rely on the responses of many spiral ganglion neurons (Gelfand, 2010). We should therefore be careful not to confuse perceptually-determined critical bandwidths with neuronal activation patterns, but critical bands can act as a liberal guideline to distinguish groups of co-activated spiral ganglion cells centered around a CF. In complex tones when components are so close together that they are within the same CB, they activate the same group of auditory neurons, while if they are in separate CB they activate different groups of auditory neurons.

In the current study, critical bandwidths determined in a notched noise experiment by Baker and Rosen (2006) were used to determine whether tones would be resolved or unresolved on the basilar membrane. In the Baker and Rosen (2006) experiment, notched noise maskers of different shapes and widths were employed to determine masked thresholds which change abruptly when the maskers extend beyond the CB. Using CB estimates, signal components can be named 'resolved' when they fall in separate CB and 'unresolved' when they are within the same CB (Micheyl & Oxenham, 2004). Of course

signals may be processed in multiple critical bands simultaneously, so may be resolved in some and unresolved in others. These signals would be called 'partially unresolved.'

1.7   Outline and goals

Based on the work of Laroche *et al.* (2013), the goal of this study is to investigate empirically whether there is a second neural initiator of the ASSR. This evidence, in turn, will shed light on periodicity envelope encoding in the auditory pathway as well as the limits of phase locking. We will accomplish these goals by measuring EFR in normal hearing adult subjects to different modulated carrier frequencies.

In the first experiment we will investigate the changes in the EFR amplitude with pairs of neighboring harmonics (i.e. the envelope frequency remains constant), with harmonic number increasing. If the response is due solely to the accepted model of cochlear initiation we expect response amplitude to increase with frequency as the components become more and more unresolved and able to interact on the basilar membrane. However, if the response reflects a central process driven by auditory nerve phase-locking to the harmonic components, we expect response amplitude to decrease with increasing harmonic number due to the well-known decrease in phase locking strength with increasing frequency. If, however, the response from resolved harmonics reflects an envelope introduced centrally and the response from unresolved harmonics reflects an envelope initiated in the cochlea (as proposed by Laroche *et al*. 2013), we would expect that the low frequency stimuli would follow the trend suggested by central EFR introduction due to their resolved nature whereas the high frequency stimuli approximate the trend of the cochlear site of initiation due to their unresolved nature. By presenting pairs of harmonics ranging from fully resolved to unresolved, we therefore expect to see an initial drop in response amplitude with increasing frequency (for the low frequency resolved harmonics), and then an increase in response amplitude with increasing frequency for the higher-frequency unresolved harmonics, giving rise to a 'U' shaped (quadratic) function. To further our theory that the EFR to resolved but not unresolved harmonics is influenced by the frequency of the components and phase locking, responses to pairs of equally resolved components (increasing in frequency) will

also be recorded. We expect similar response amplitudes with these equally resolved stimuli compared to the resolved harmonics of 215 Hz but not the unresolved harmonics.

In the second experiment, we will attempt to obtain similar results to Experiment 1 with a single stimulus containing pairs of tones that are not harmonically related, such that each pair will give rise to an EFR at a different modulation frequency. This will be achieved by either increasing or decreasing the frequency separation of each subsequent pair by 6 Hz. The amplitude of these responses, by component frequency, will be compared with those of Experiment 1 to determine if it is feasible to gather all of this information in a short amount of time.

In the third experiment, we will seek to obtain additional evidence for the existence of both cochlear and neural (or beyond the basilar membrane) components to the EFR by manipulating frequency distance and component phase. High and low carrier frequencies will be used to control the amount of phase-locking (based on the well-known decrease in auditory nerve phase-locking with increasing frequency) and two modulation rates will be used to control whether the presented tones will be resolved or unresolved. If the EFR is initiated beyond the cochlea for resolved tones, we hypothesize that responses for resolved tones will be much lower in amplitude (or absent) at a high carrier frequency. In this condition, cochlear interaction should not occur due to the highly resolved (or spaced) nature of the tones and neural introduction should be poor or not possible due to the fact that the tones are too high frequency to be robustly temporally encoded in the auditory nerve. For unresolved tones, we expect the EFR to be present for both low and high carrier frequencies. If the longstanding "cochlear-only" initiation theory is correct, we should have no EFR measured when components are well resolved, no matter whether the carrier frequency is within the range of phase locking or not, due to the fact that basilar membrane interaction is required for envelope introduction. Each modulated stimulus will also be recorded in pairs and alone to investigate the feasibility of time-saving measures to assess responses to both unresolved and resolved components simultaneously.

To further our investigation of the EFR initiators for resolved and unresolved tones, we will minimize the depth of the modulation on the basilar membrane by shifting the phase of the centre component frequency by 90 degrees; this is called quadrature phase. If the accepted cochlear-only initiation theory is correct, quadrature phase should severely reduce or eliminate the EFR. However, if the envelope for resolved tones is initiated centrally based on temporal activity in the auditory nerve, as we hypothesize, quadrature phase should have much less impact on the EFR for resolved tones. This is because a central interaction must occur after cochlear transduction and the phase relationship between the components will have been shifted by the well-known frequency-latency function on the basilar membrane. However, quadrature phase may reduce responses to resolved tones if there is some degree of overlap (i.e. if the tones are not fully resolved).

CHAPTER 2   METHODS

2.1   Subjects

Twelve normal-hearing subjects aged 23-41 years (one male) participated in Experiments 1 and 2; while ten normal-hearing subjects aged 23-27 years (all female) participated in Experiment 3. All subjects indicated no neurological conditions or abnormalities.

2.2   Stimuli

2.2.1   Experiment 1

The first experiment measured responses to pairs of stimuli that were harmonics of a common fundamental frequency and also to pairs of stimuli that were designed to be roughly equidistant on the cochlea. For the common-fundamental stimuli, ten pairs of harmonics with an f_0 of 215 Hz were used, with increasing harmonic number. The lower harmonic ranged from the 3rd to the 12th and the higher harmonic was always one greater (i.e. the 4th to the 13th; Table 1). All harmonic components were adjusted individually to produce 70 dB SPL at the cochlea, based on the middle ear transfer function specified in ANSI 53.4 (2007; Table 3).

Table 2. Stimuli used in Experiment 1a envelope following response recording. All stimuli are pairs of harmonics of 215 Hz (3rd-13th).

	Component 1 (Hz)	Component 2 (Hz)	Harmonic #	Harmonic #	f_0
Stim1	645	860	3	4	215
Stim2	860	1075	4	5	215
Stim3	1075	1290	5	6	215
Stim4	1290	1505	6	7	215
Stim5	1505	1720	7	8	215
Stim6	1720	1935	8	9	215
Stim7	1935	2150	9	10	215
Stim8	2150	2365	10	11	215
Stim9	2365	2580	11	12	215
Stim10	2580	2795	12	13	215

The equally resolved stimuli were the 3rd and 4th harmonics of an increasing f_0 (215 Hz, 322.5 Hz, 430 Hz, 537.5 Hz and 645 Hz). The second harmonic in each pair was also a harmonic of 215 Hz (Table 2). As with the harmonics of 215 Hz, these components were individually adjusted to be 70 dB SPL at the level of the cochlea, based on the middle ear transforms specified in ANSI 53.4 (2007; Table 3).

Table 3. Stimuli used in Experiment 1b envelope following response recording. All stimuli are the 3rd and 4th harmonic of a different modulation frequency chosen so that the upper component is a harmonic of 215 Hz and all components are resolved. Critical band (CB) widths were estimated using results by Baker and Rosen (2006).

	f_0 (Hz)	Component 1 (Hz)	Component 2 (Hz)	Harmonic #	Harmonic #	Harmonic # (215 Hz)	Harmonic # (215 Hz)
Stim1	215	645	860	3	4	3	4
CB width		158.6	185.7				
Stim11	322.5	967.5	1290	3	4		6
CB width		199.2	239.9				
Stim12	430	1290	1720	3	4	6	8
CB width		239.9	294.0				
Stim13	537.5	1612.5	2150	3	4		10
CB width		280.5	348.2				
Stim14	645	1935	2580	3	4	9	12
CB width		321.1	402.4				

2.2.2 Experiment 2

Two pseudo-harmonic stimulus 'bundles' were designed such that each pair of tones was separated by a different distance, corresponding to a different f_0. One of these bundles, called 'Increasing' was designed such that the first two components were separated by 215 Hz, but each subsequent component was separated by an additional 6 Hz (e.g., 221 Hz between component 2 and 3, 227 Hz between component 3 and 4). A second 'Decreasing' bundle was designed such that the widest spacing was for the lowest pair of components (269 Hz) and the spacing became narrower by 6 Hz between each subsequent pair. The stimuli are described more fully in the following table (Table 3). All harmonic components were again adjusted individually using the middle ear transfer

function (ANSI 53.4 (2007); Table 3) in order to be equivalent in level at the cochlea (70 dB SPL).

Table 4. Stimuli used in Experiment 2 envelope following response recording. Each stimulus has ten frequency components with the distance between each component (f_0) increasing or decreasing by 6 Hz.

Increasing Bundle (Hz)	645	860	1081	1308	1541	1780	2025	2276	2533	2796
$f_{0\ (Hz)}$	215		227		239		251		263	
	■	221		233		245		257		■
Decreasing Bundle (Hz)	645	914	1177	1434	1685	1930	2169	2402	2629	2850
$f_{0\ (Hz)}$	269		257		245		233		221	
	■	263		251		239		227		■

2.2.3 Experiment 3

Sinusoidally amplitude modulated (SAM) tones were created with two carrier frequencies, 1008 and 3024 Hz, each modulated at 74 and 518 Hz (Table 4). Cochlear resolution estimates were made using the cut-off frequencies found by Baker & Rosen (2006). At this presentation level the 1008 Hz carrier would be unresolved approximately from 908.65 Hz to 1091.35 Hz and the 3024 Hz carrier from 2755.6 Hz to 3244.4 Hz. Each of these stimuli was also created in quadrature phase whereby the centre component is shifted forward in phase by 90° relative to the sidebands to minimize the depth of the stimulus modulation envelope. The amplitude of the sidebands were always 50% of the centre band. Stimuli were presented at 70 dB SPL.

Table 5. Stimuli presented in the envelope following response recorded in Experiment 3. Carrier frequencies of 1008 and 3024 Hz were each modulated at 74 and 518 Hz in common and quadrature phase.

Lower component frequency (Hz)	Carrier frequency (Hz)	Upper component frequency (Hz)	Modulation frequency (Hz)	Cochlear resolution
934	1008	1082	74	unresolved
490	1008	1526	518	resolved
2950	3024	3098	74	unresolved
2506	3024	3542	518	resolved

2.3 Procedure- Envelope Following Response

Stimuli were presented binaurally from a National Instruments PXI 4461 Dynamic Signal Acquisition card through a GSI-61 audiometer, and routed via ER-3 type insert earphones. Subjects relaxed with eyes closed in the supine position while electrophysiological responses were recorded between Cz and the mid-posterior neck using gold-plated Grass electrodes. The ground electrode was placed at Fpz for Experiments 1& 2 and the left mastoid in Experiment 3. All inter-electrode impedances were below 5 kΩ and were within 2 kΩ of each other. Responses were filtered between 30 and 3000 Hz and amplified 50,000 times with a Grass LP-511 biopotential amplifier and then digitized at 16 kHz by an M-series PXI card sharing a digital clock with the stimulus presentation card.

Data for Experiments 1 and 2 were collected in the same session. Data for Experiment 3 was collected in a separate session. Each stimulus was presented in two separate blocks (i.e. one block for each polarity), with block order randomized within each experiment. Stimuli were presented continuously in 1 second sweeps, with a rejection threshold set to 25 µV. For Experiments 1 and 2, each stimulus was presented

until 150 sweeps were accepted in each polarity (2.5 minutes). For Experiment 3, each stimulus was presented until 240 sweeps were accepted in each polarity (4 minutes).

2.4 Data Analysis

All analyses were completed in MATLAB (The Mathworks, Natick MA) and R (R Core Development Team). Data were first re-averaged in longer sweeps in order to improve frequency resolution. Data for Experiments 1 and 2 were averaged in 15 ten-second sweeps, providing 0.1 Hz resolution. Data for Experiment 3 were averaged in 15 sixteen-second sweeps, providing $1/16^{th}$ Hz resolution. Raw amplitudes were calculated at envelope frequencies for each polarity average, the alternating polarity average ((polarity 1 + polarity 2)/2), and the difference average ((polarity 1 – polarity 2)/2). These averages were corrected for noise-related bias by multiplying each value by the following formula from Picton, Dimitrijevic, Perez-Abalo, & Van Roon (2005):

$$\frac{1}{1 + .965e^{-1.348X} + .078e^{-0.285X}}$$

where X is the estimated level of the noise. Noise estimates were calculated as average response amplitude 10 Hz above and below target responses for single responses and 5 Hz above and below for bundled responses. Values were calculated for individual subjects and also for the grand average response. Repeated measures ANOVAs on either corrected amplitude or signal-to-noise ratio data (or both) were conducted for Experiments 1 and 2. Post hoc testing included paired t-tests on SNR and corrected amplitude responses. SNR was preferred to response amplitude for comparing results across multiple f_0 frequencies due to the well-known relationship between frequency and response amplitude. Responses from one subject were removed from the SNR analysis due to their status as extreme outliers (on average, responses for this subject were 5.9 standard deviations above mean scores in each condition). This subject is also known to have very large ABR responses for an unknown reason. A repeated measures ANOVA was conducted on data from Experiment 3 to determine the main and interaction effects

21

between modulation frequency, carrier frequency, phase, and presentation mode (i.e. stimuli presented in isolation or in pairs). Post-hoc testing included paired t-tests with Bonferroni correction. All statistical measures were conducted and all figures generated using MATLAB or R.

CHAPTER 3   RESULTS

3.1   Experiment 1a- Equally spaced in Hz

3.1.1   *Rationale*

Responses to pairs of harmonics of 215 Hz (3rd and $4^{th} \rightarrow 12^{th}$ and 13th harmonics) are measured to investigate how resolution and frequency of the components affect EFR response amplitude. Harmonics 3-7 are believed to be resolved while harmonics 10-13 unresolved, with the intermediate harmonics being partially unresolved. We hypothesize that response amplitude will decrease with increasing frequency for resolved harmonics and increase with increasing frequency for unresolved harmonics, such that responses for the lowest and highest harmonic pairs will be higher than for the middle harmonic pairs.

3.1.2   *Results*

A summary of responses can be found in Figures 1 and 2. A repeated measures ANOVA on corrected amplitudes was conducted with harmonic number as the independent variable. Mauchly's test indicated that the assumption of sphericity was not met (p=0.00000001) so Greenhouse-Geisser corrections were used. A significant effect of harmonic number on EFR amplitude was found ($F_{(2.22,24.45)}$=28.698, p=0.000002, η^2=0.534). Post-hoc t-tests were computed to compare response amplitudes for the lowest two harmonic pairs (harmonics 3-5) with the middle two harmonic pairs (harmonics 7-9) and the highest two harmonic pairs (harmonics 11-13). The lowest two harmonic pairs were significantly greater in amplitude than the middle two harmonic pairs ($t_{(23)}$=9.051, p=0.000000005, Bonferroni corrected α=0.016; grand average slope= -0.1866). This decrease in response amplitude with increasing harmonic number was reversed, however, for the unresolved harmonics: the two middle harmonic pairs were significantly smaller in response amplitude than the final two pairs ($t_{(23)}$=4.824, p=0.00007, Bonferroni corrected α=0.016). The last two harmonic pairs were also significantly smaller in

23

response amplitude than the first two ($t_{(23)}$=8.06, p=0.00000004, Bonferroni corrected α=0.016). When response amplitudes were plotted by upper harmonic frequency, a quadratic function fit the results best (R^2=0.51; Figure 1).

Figure 1. Envelope following response amplitudes to pairs of harmonics of 215 Hz (3rd-13th) measured from twelve normal hearing individuals. **A/** Individual responses are shown in grey while the grand average is shown in black. The percentages of responses significantly greater than the noise are also shown. **B/** Line of best-fit with an R^2= 0.51.
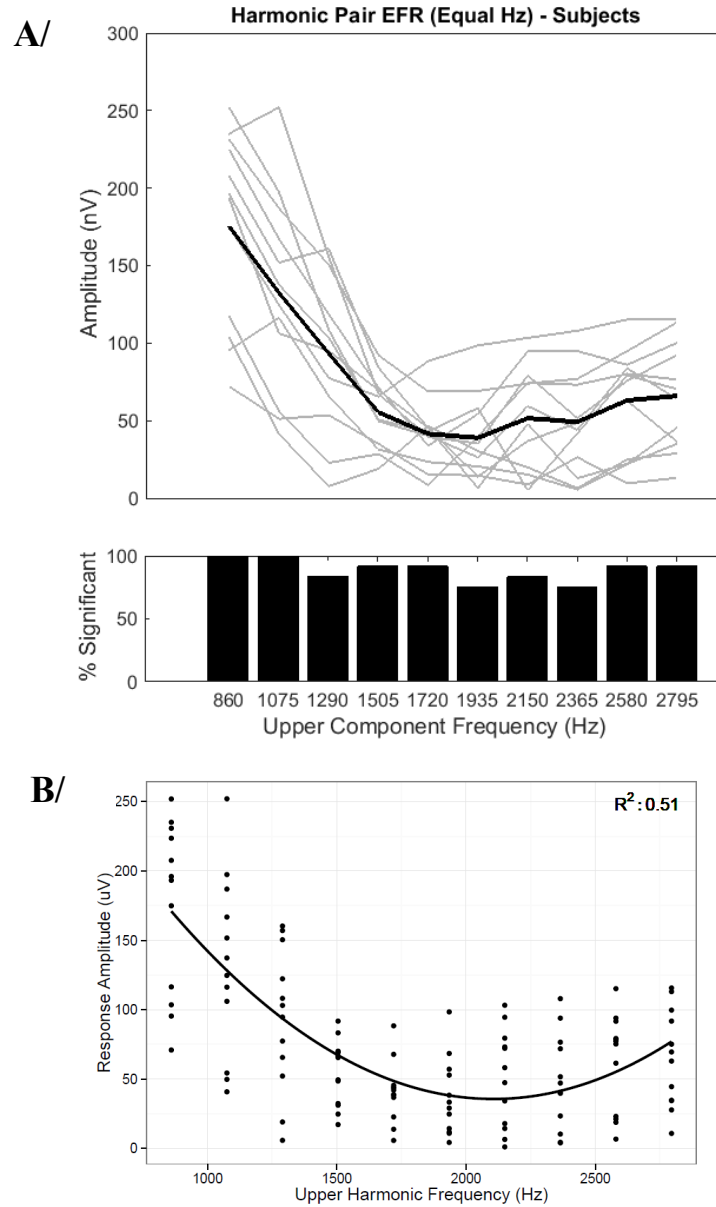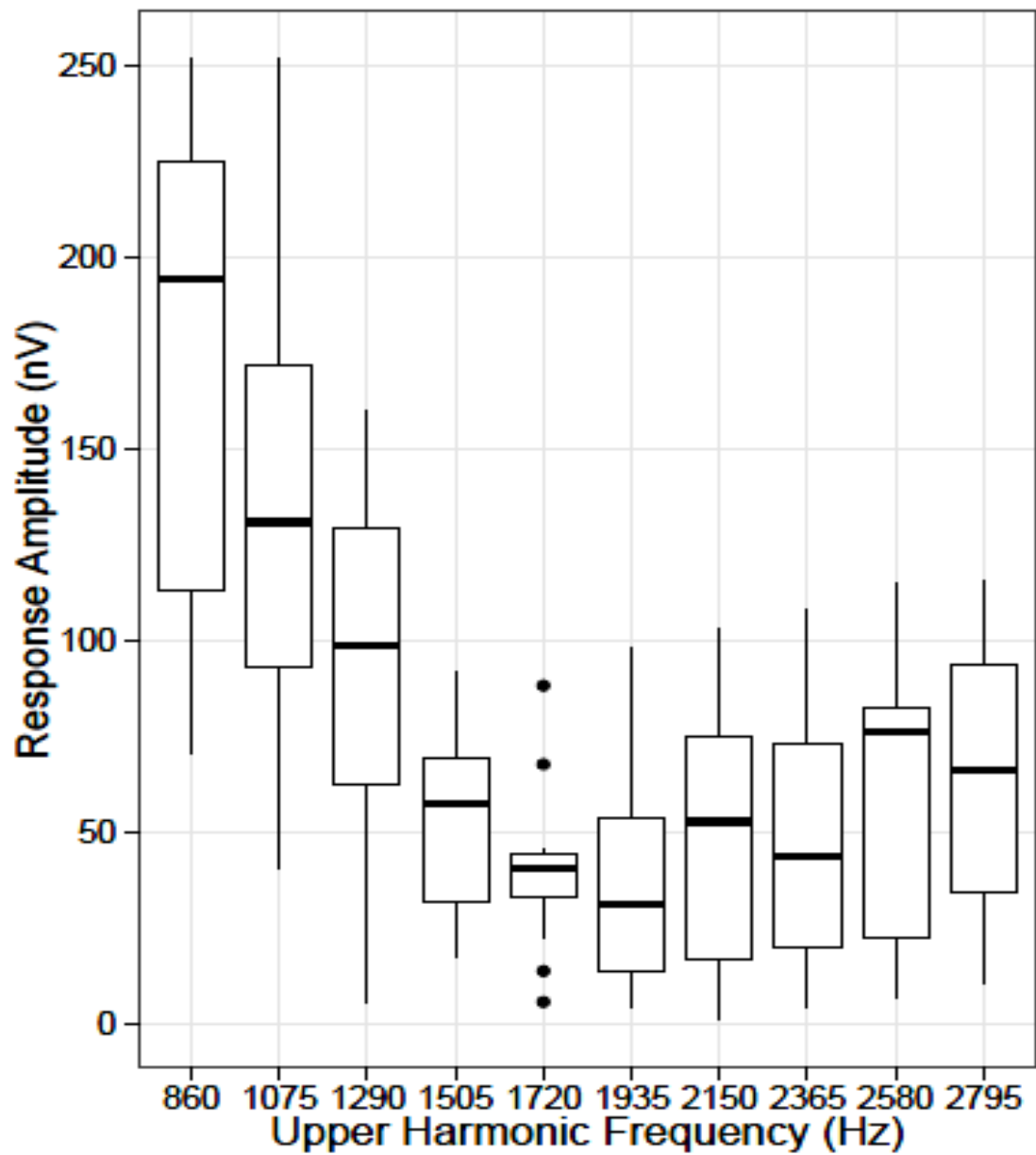
Figure 2. Envelope following response amplitudes to pairs of harmonics of 215 Hz (3rd-13th) measured from twelve normal hearing individuals shown as box-and-whisker plots. Thick horizontal lines represented the median and thin horizontal lines represent the median of the upper and lower quartiles. Vertical lines represent the range of responses.

25

Repeated measures ANOVA and post-hoc tests were also conducted on the signal-to-noise ratios (SNR; see Figure 3), as opposed to corrected amplitudes discussed above. One subject was omitted from these analyses due to their response SNR being outliers in 7/10 conditions (>3 SD from mean). The repeated measures ANOVA using SNR data also found a significant effect of harmonic number on SNR ($F_{(2, 20)}=35.445$, $p=0.0000003$, $\eta^2=0.382$). A decrease in SNR with harmonic number (first two pairs versus middle two pairs) was found as before using the t-test ($t_{(21)}=8.428$, $p=0.00000004$, Bonferroni corrected $\alpha=0.01$) and the rise after the middle stimulus was also found to be significant ($t_{(21)} = 4.295, p = 0.0003$). In agreement with the corrected amplitudes t-test, the last harmonic pair was significantly smaller in SNR than the first two ($t_{(21)}=7.215$, $p=0.0000004$, Bonferroni corrected $\alpha=0.01$).
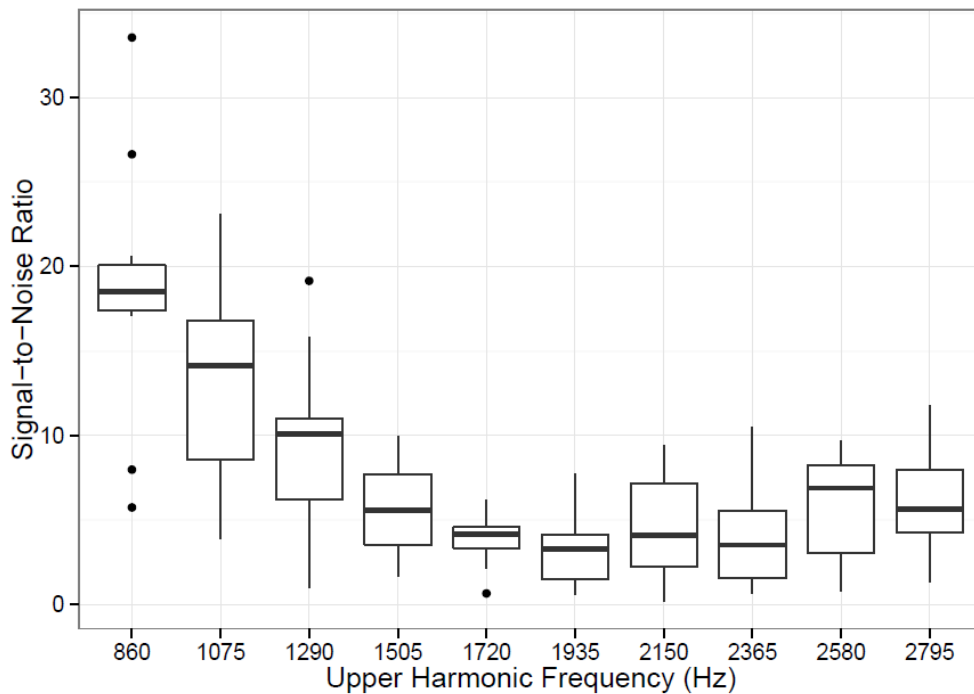

Figure 3. Envelope following response signal-to-noise ratios to pairs of harmonics of 215 Hz (3rd- 13th) measured from eleven normal hearing individuals shown as box-and-whisker plots. One subject was excluded from this dataset due to their status as an outlier (>3 SD from mean in 7/10 conditions). Thick horizontal lines represented the median and

thin horizontal lines represent the median of the upper and lower quartiles. Vertical lines represent the range of responses.

3.1.3 Discussion

Upon preliminary inspection of the data it is clear that more than cochlear interaction is involved in introducing the EFR response (see Figures 1 & 2). The largest responses are to the most highly resolved components, which in this case are the lowest frequencies. It is possible that resolved responses are generally more robust or that we did not measure responses to components that were unresolved enough to generate as large of a response. If one assumes no overlap in the cochlea for fully resolved components, EFR responses to resolved components should be non-existent if cochlear interaction is the sole mechanism for introduction of energy at the envelope frequency. Even if there is some interaction for these resolved components, the resolved responses should be smaller than the unresolved responses, which was not found. There was an increase with increasing frequency for unresolved components, suggesting that cochlear interaction is responsible for introducing the envelope for these harmonics. The pattern obtained was "U" shaped as hypothesized, and was best fit by a quadratic function (R^2=0.51).

We propose two different origins for the EFR response: the accepted model of cochlear interaction for unresolved stimuli and a central interaction for resolved stimuli that depends on an individual's ability to phase lock to the components. If the EFR arises due to central interaction of resolved components we would see a decrease in response (due to a decrease in phase locking ability) with increasing frequency until the components are no longer resolved. It is generally believed that harmonic stimuli start to become unresolved around the 7th harmonic, corresponding to the 1505/1720 Hz harmonic pair in this experiment. When the lowest frequency stimulus was compared to the 7th harmonic a significant decrease in response amplitude was found for both corrected amplitudes and SNR evaluations, supporting our claim that resolved components introduce EFR at a region more medial than the basilar membrane.

If the EFR also arises due to cochlear interaction, we would see increasing response as components become more and more unresolved and able to interact on the

27

basilar membrane (higher frequencies). Upon visual inspection, it appears that the responses increase again after the 7th harmonic. It should also be noted that the response to the lowest frequency stimulus was significantly larger than the response to the highest frequency stimulus when determined by both SNR and corrected amplitude data. Based on these results we would suggest that cochlear interaction is occurring to introduce EFR energy for the high frequency unresolved components.

3.2   Experiment 1b- Equal cochlear spacing

3.2.1   Rationale

To investigate the effect of carrier frequency on EFR response amplitude separate from cochlear resolution, stimuli expected to be roughly equally resolved were used. This was accomplished by using the 3rd and 4th harmonics of increasing f_0.

3.2.2   Results

Response amplitudes (corrected values) decreased with increasing component frequency (Figure 4). A repeated measures ANOVA found a significant effect of harmonic number on response amplitude ($F_{(1.64,\ 18.04)}$=69.215, p=0.00000001, η^2=0.785; after the values had been corrected for sphericity violation (p=0.0001) using Greenhouse-Geisser) and SNR ($F_{(4,40)}$=18.76, p=0.000000009, η^2=0.492). Experiment 1a and Experiment 1b were plotted for comparison (Figure 5) using SNR, since response amplitudes and noise decrease with increasing frequency. When the SNR for the envelope response to the 11th and 12th harmonics of 215 Hz (i.e. 2365 and 2580 Hz) was compared with the SNR for the response to the highest equal cochlear spacing pair (1935 and 2580 Hz), the latter was found to have a significantly smaller SNR ($t_{(10)}$=3.222, p=0.009, Bonferroni corrected α=0.01).
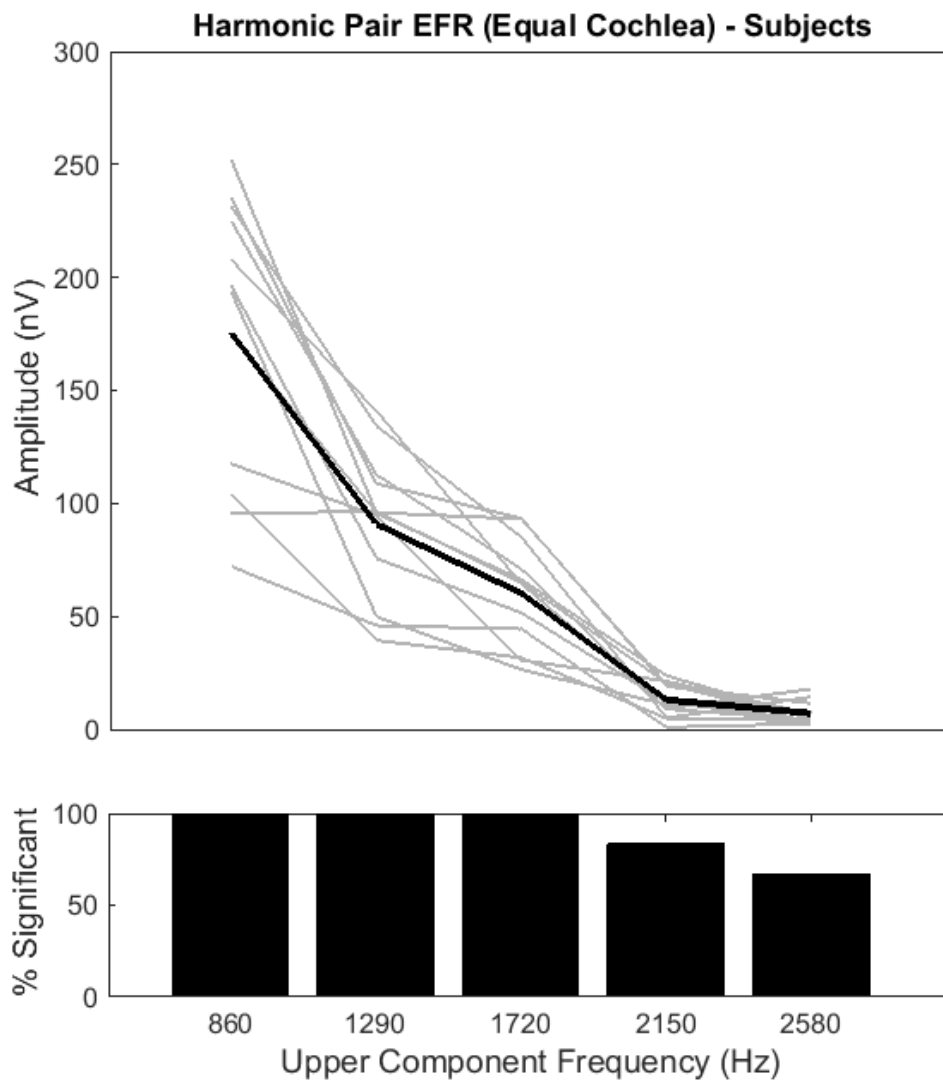
Figure 4. Envelopes following response amplitudes to pairs of harmonics of equal cochlear resolution were measured from twelve normal hearing individuals. Individual responses are shown in grey while the grand average is shown in black. The percentages of responses significantly greater than the noise are also shown.

Harmonic Pair EFR
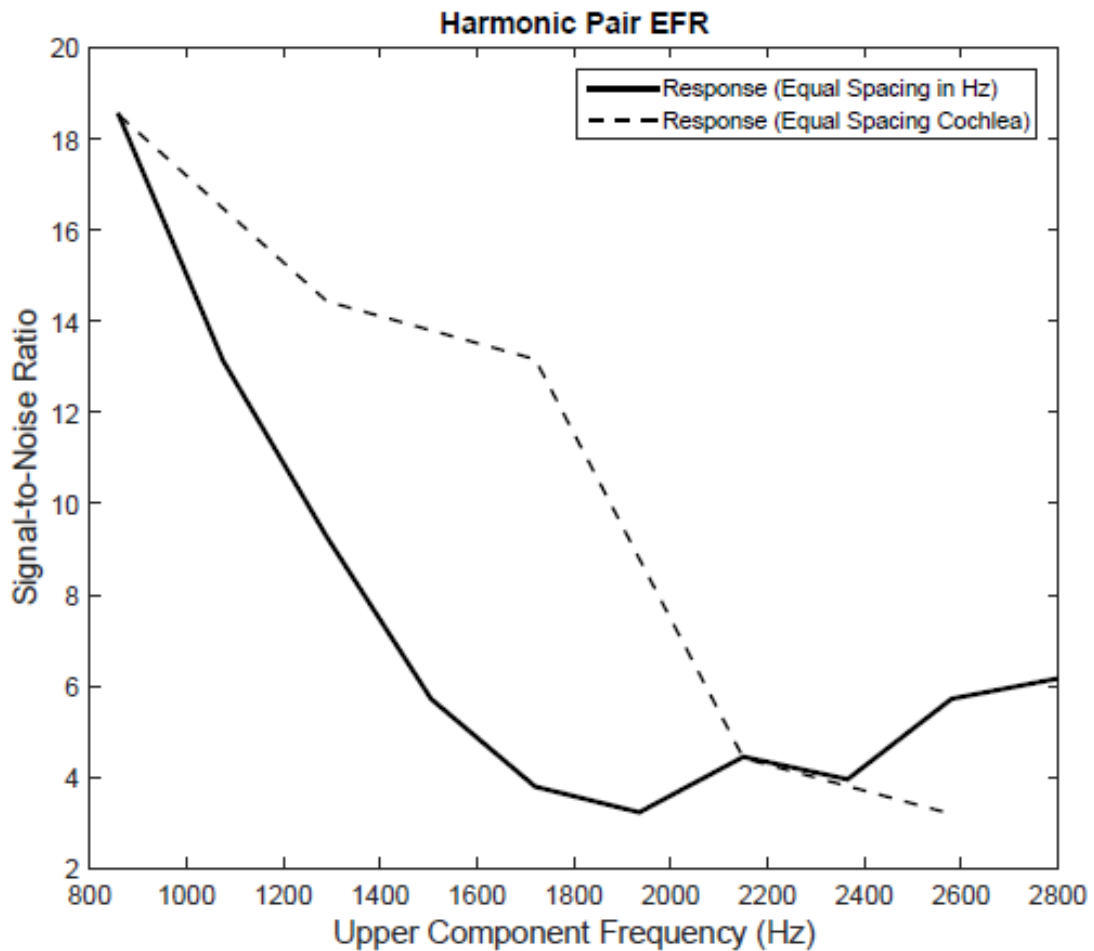
Figure 5. Envelope following response signal-to-noise ratios to pairs of harmonics of 215 Hz (3rd- 13th; black) and equal cochlear resolution (dashed line) measured from eleven normal hearing individuals. One subject was excluded from this dataset due to their status as an outlier (>3 SD from mean in 7/10 conditions).

3.2.3 Discussion

Based on our model of resolved harmonic EFR being introduced centrally, it is clear that phase locking should be essential for initiating a response. By keeping the components equally resolved, as was done in this experiment, we investigated whether

the responses decrease with increasing frequency, as is consistent with the phase locking dynamics of the auditory nerve. There was a significant decrease in response amplitude between the lowest frequency stimulus and the highest frequency stimulus when corrected amplitudes were used ($t_{(11)}$=9.474, p=0.000001, Bonferroni corrected α=0.01). This lends further support to the claim that the decrease in response with increase in frequency of the resolved components is due to phase locking.

Other evidence for the hypothesis that unresolved and resolved components introduce EFR in different ways was found by the significant difference between the highest equally resolved component frequency from this experiment and the second highest unresolved component from Experiment 1a- these stimuli have the same upper component frequency. Since the response to the equally resolved component is driven down by phase locking limits, another process must be occurring in the unresolved components of Experiment 1a to cause a significantly larger response. The main difference between the two conditions is the resolution of their components; therefore it is likely that the rise in EFR response in the unresolved condition is because of cochlear interaction.

3.3   Experiment 2- Bundled with increasing and decreasing spacing

3.3.1   Rationale

We investigated the amplitude differences of the responses to individual pairs of components across a range of frequencies compared to all of those components bundled together with f_0s increasing or decreasing by 6 Hz with each component. This experiment was done to explore whether the U shape function found in Experiment 1a could be obtained using one stimulus instead of ten. Also, presenting the pairs simultaneously reduces the possibility of significant off-frequency encoding.

3.3.2   Results

Repeated measures ANOVAs found a significant effect of harmonic number on response amplitude with increasing ($F_{(2.912, 32.032)}$=8.101, p=0.0004, η^2=0.341) and

decreasing ($F_{(3.344, 36.784)}$=20.784, p=0.00000002, η^2=0.637) f_0 stimuli when corrected amplitudes were used (Figures 6 & 7). Sphericity corrections were made with these results (p<0.05). A quadratic function was found to fit the increasing f_0 data best (R^2=0.2; Figure 8) whereas it was not a good fit for the decreasing f_0 data (R^2=0.01; Figure 9). SNR values were used in post-hoc t tests to investigate trends in the bundled results with increasing f_0 only. A significant decrease was not found (p>0.05) when comparing the lowest pair (645 Hz, 860 Hz) to the middle pair (1541 Hz, 1780 Hz). However, the SNR was seen to significantly increase from the middle pair to the highest pair (2533 Hz, 2796 Hz) ($t_{(10)}$=3.968, p=0.00265, Bonferroni corrected α=0.01).
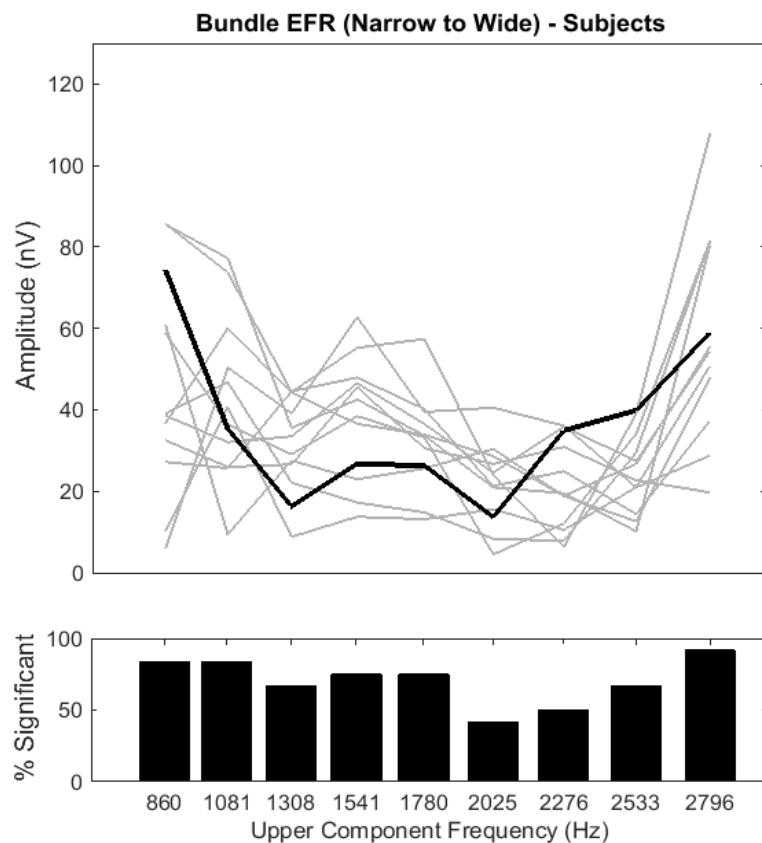
Figure 6. Envelope following responses to a bundled stimulus with an increase in component spacing from 215-263 Hz (6 Hz increase between each component) as the frequency increases. Individual responses are shown in grey while the grand average is

shown in black. The percentages of responses significantly greater than the noise are also shown.
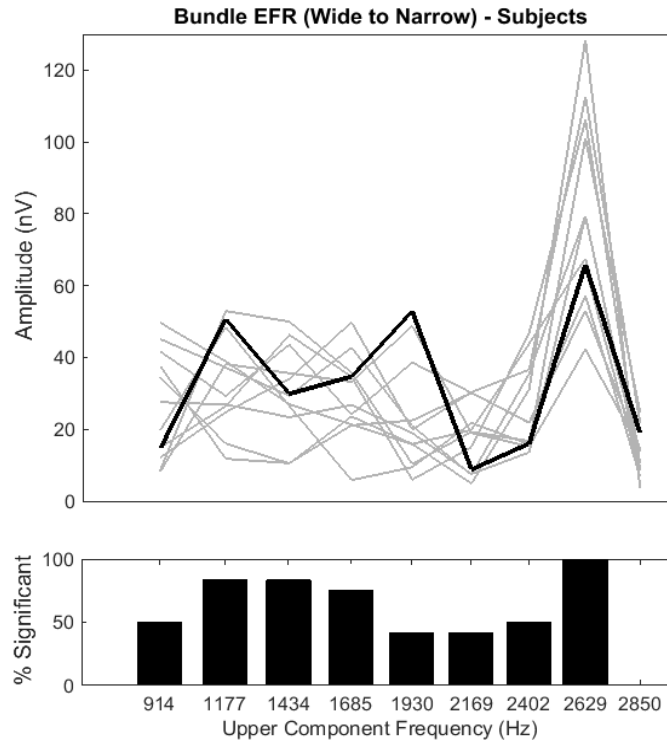
Figure 7. Envelope following responses to a bundled stimulus with a decrease in component spacing from 269-221 Hz (6 Hz decrease between each component) as the frequency increases. Individual responses are shown in grey while the grand average is shown in black. The percentages of responses significantly greater than the noise are also shown.
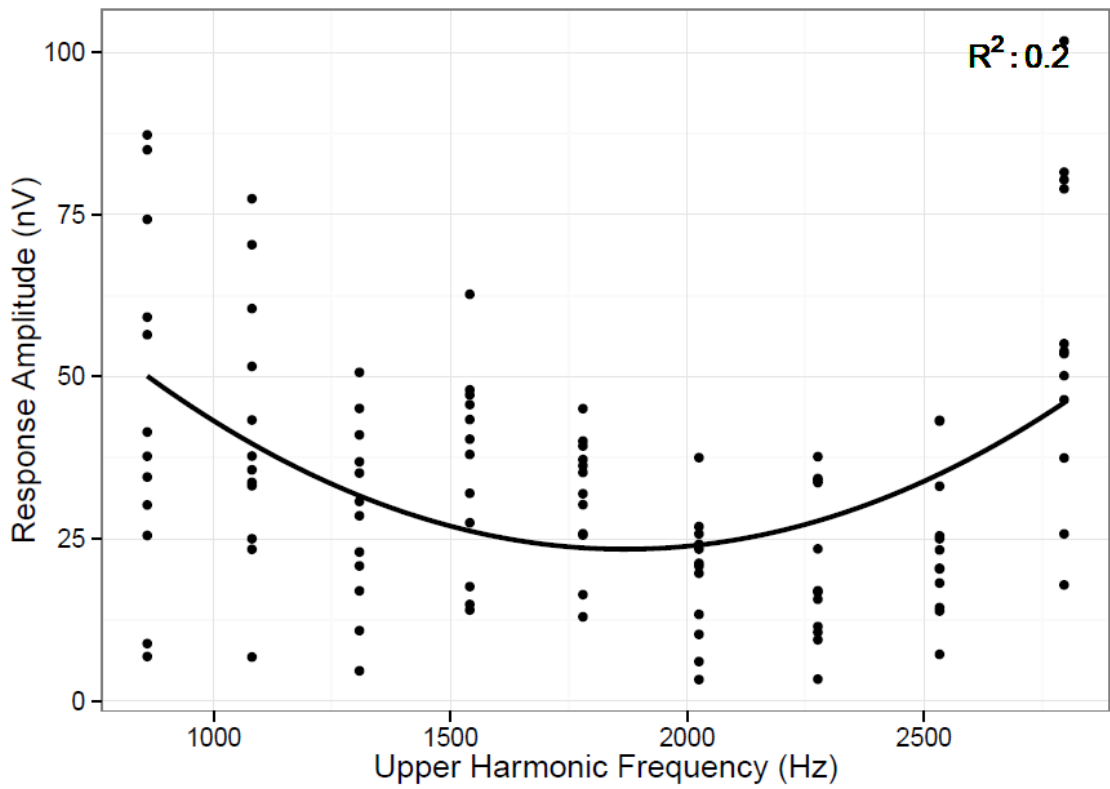
Figure 8. Envelope following responses to a bundled stimulus with an increase in component spacing from 215-263 Hz (6 Hz increase between each component) as the frequency increases. Line of best fit was included with an R^2=0.2.
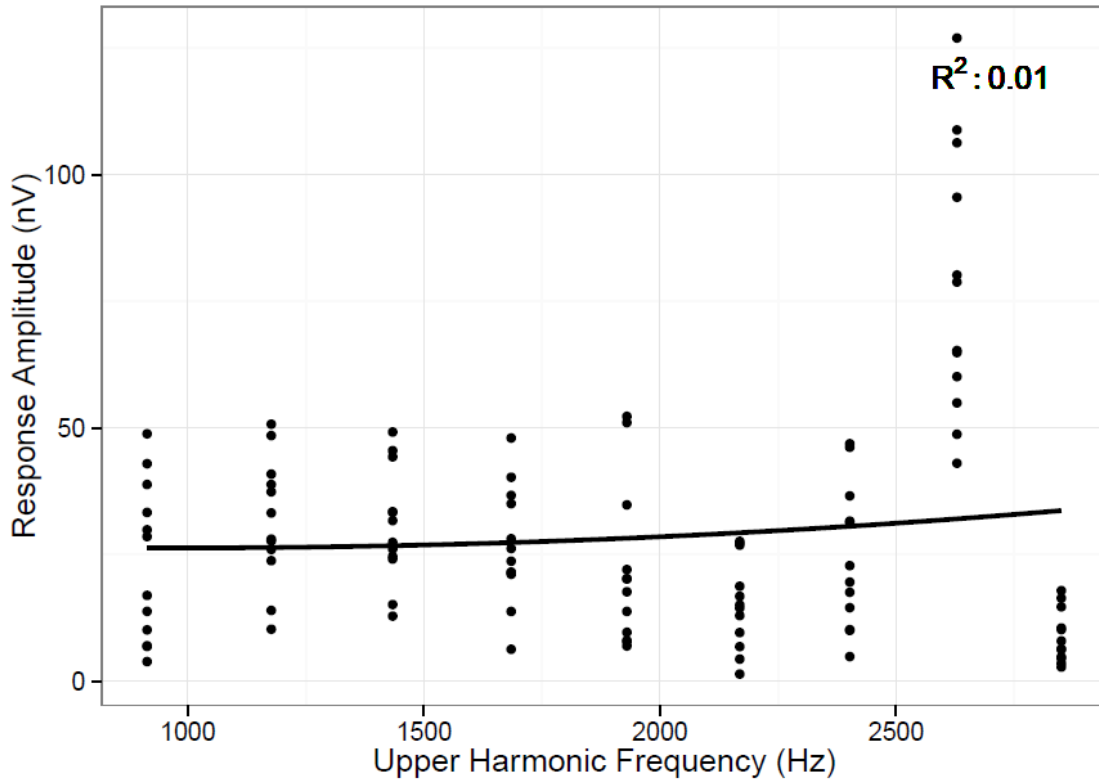
Figure 9. Envelope following responses to a bundled stimulus with a decrease in component spacing from 269-221 Hz (6 Hz decrease between each component) as the frequency increases. Line of best fit was included with an R^2=0.01.

To investigate whether the bundled increasing f_0 data approximates the function found in Experiment 1a SNR values were compared between Experiments 1a and 2 in each subject. No significant difference was found between data sets in the middle or highest component responses (p>0.05) but there was a significant difference in the response to the lowest pair ($t_{(10)}$=6.873, p=0.00004, Bonferroni corrected α= 0.01). Correlations between the two data sets revealed r=0.330 overall.

3.3.3 Discussion

In general we found that the bundled stimuli with increasing f_0 with frequency approximated the results found when pairs of components were presented individually

(Experiment 1a). When first inspecting this bundled data the general U shape found in Experiment 1a was seen and a quadrature function was found to fit the data best. There was a significant increase from the middle harmonic to the upper harmonic but no significant decrease (with frequency) was seen in the low frequency pairs, indicating that the latter half of the U was better maintained in the bundled data. This suggests that the EFR for resolved pairs presented in isolation (Experiment 1a) is driven by processes that are more widely tuned, such as the converging input found in the central auditory system, than for unresolved pairs. When the bundled and unbundled data were compared overall a correlation of 0.330 was found with no significant difference in the amplitudes of the middle and upper frequency responses. Together, these results suggest that presenting many component frequencies with increasing f_0 simultaneously does give comparable information to presenting pairs individually in the higher unresolved components, giving us a method to possibly investigate EFR initiated through cochlear interaction in very little time. Responses to resolved components may require more separation, however.

Interestingly, the bundled stimulus with decreasing f_0 did not show any generalizable trend at all and the quadratic function that fit the increasing f_0 data did not approximate these results. In this condition the low frequencies would be even more resolved than in the increasing f_0 condition because the spacing between components is larger in the frequency range where cochlear filters are the smallest. The same can be said for the unresolved being even more unresolved in this condition than the increasing f_0 condition. It is unclear why the decreasing f_0 stimulus gave such results. It is a complex stimulus, therefore, interactions between components and responses, as well as changing cochlear filters in the brainstem nuclei, may have influenced the EFR measured. More research should be conducted to tease apart these issues.

3.4 Experiment 3a- SAM phase manipulation

3.4.1 Rationale

The stimuli in this study were selected to see if an EFR could be obtained to stimuli that were very well resolved and if a well-resolved response could be obtained at

frequencies beyond which an FFR can be obtained (but within the limits of auditory nerve phase locking). To this end, two carrier frequencies (1008 Hz and 3024 Hz) were each modulated at 518 Hz and 74 Hz. We hypothesized that responses would be obtained for both carrier frequencies for the 74 Hz modulator, which is associated with unresolved sidebands. For the 518 Hz modulator, all components should have been well resolved for both carrier frequencies. We hypothesized that responses would be obtained for the 1008 Hz carrier and would be absent for the 3024 Hz carrier due to phase locking limits in the auditory nerve.

A phase manipulation was also employed. Shifting the centre of three components by 90° minimizes the depth of the stimulus envelope and the depth of the envelope on the basilar membrane at any single point. This manipulation is known as quadrature phase. We hypothesized that EFR arising due to cochlear interaction would be negatively impacted by the use of quadrature phase, while responses to resolved responses would be minimally impacted.

3.4.2   Results

Based on grand average responses, all responses were significantly greater than the noise except for the 3024 Hz carrier modulated at 74 Hz when quadrature phase was used. See Figure 10. A repeated measures ANOVA revealed significant effects of modulation frequency ($F_{(1,9)}$=26.959,p=0.0006,η^2=0.367), carrier frequency ($F_{(1,9)}$=14.425,p=0.004,η^2=0.055), and phase ($F_{(1,9)}$=20.460,p=0.001,η^2=0.2388) as well as significant interaction effects of modulation frequency by phase ($F_{(1,9)}$=18.815,p=0.002,η^2=0.194) and carrier frequency by phase ($F_{(1,9)}$=7.351,p=0.024,η^2=0.006). Paired t-tests showed a significantly lower response amplitude with quadrature phase than common phase for the unresolved conditions (74 Hz modulation; $t_{(9)}$=4.473, p=0.002) but not for the resolved conditions (518 Hz; p>0.05). This can be seen graphically in the Figure 11. It was also found that response amplitudes were significantly smaller in quadrature phase compared to common phase for both 1008 Hz ($t_{(9)}$=5.218, p=0.0006) and 3024 Hz ($t_{(9)}$=3.673, p=0.005) carrier frequencies as shown graphically in Figure 12.
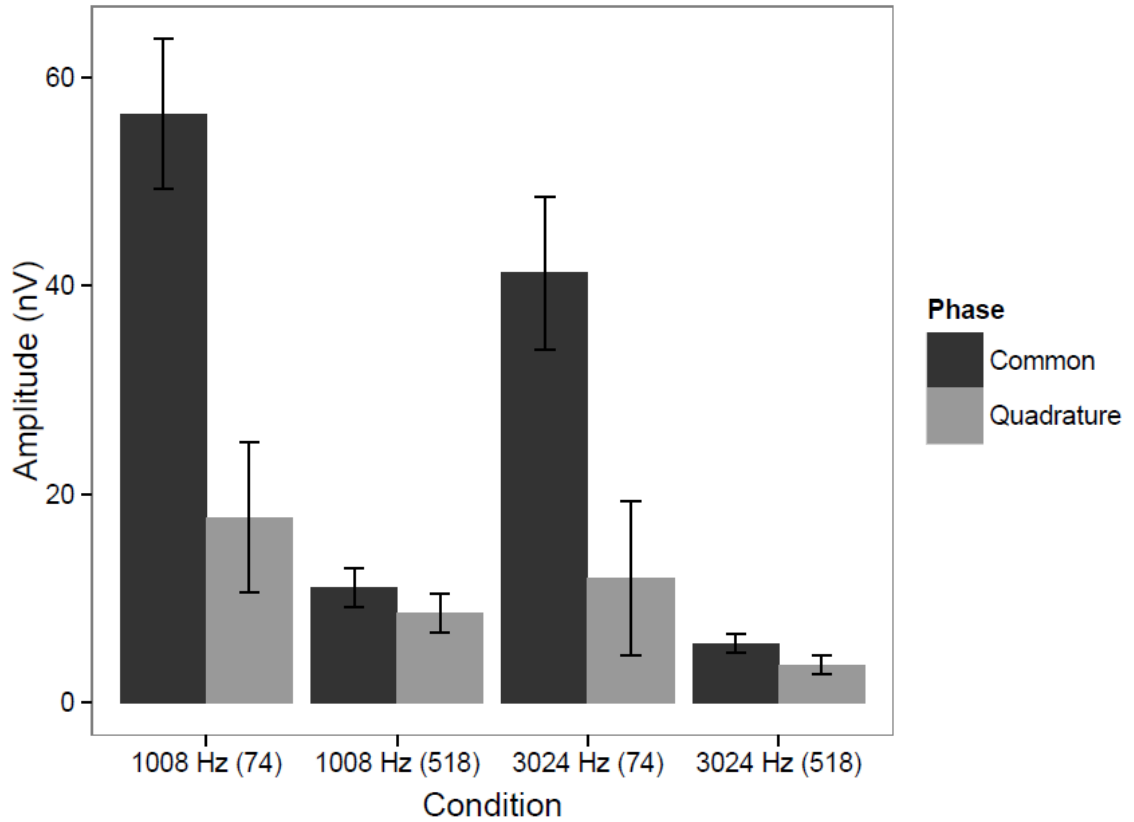
Figure 10. Envelope following response amplitudes to two carrier frequencies (1008 Hz, 3024 Hz) each modulated at rates of 74 Hz and 518 Hz, in normal and quadrature phase. Responses to quadrature phase stimuli (90° phase shift forward of the central component reduces the periodicity envelope) are shown in grey.
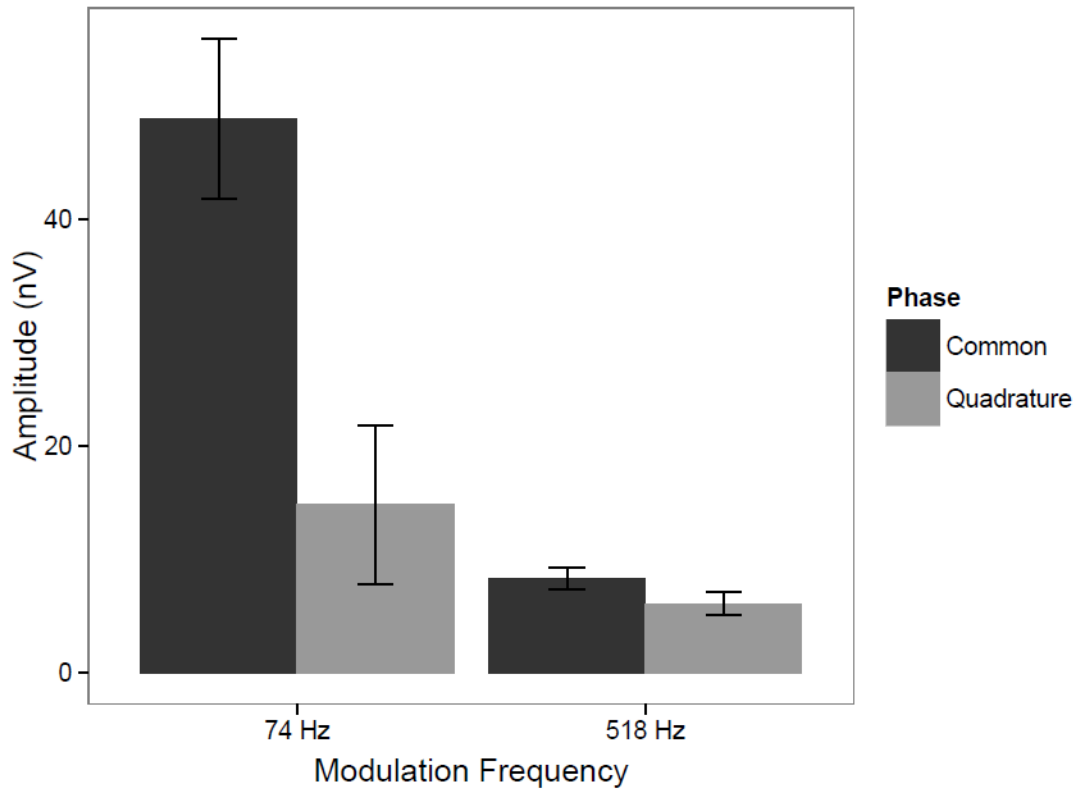
Figure 11. Envelope following response amplitude at two modulation frequencies in both common and quadrature phase. Results were collapsed across carrier frequency (1008 & 3024 Hz). Ten individuals with normal hearing were included in this data.
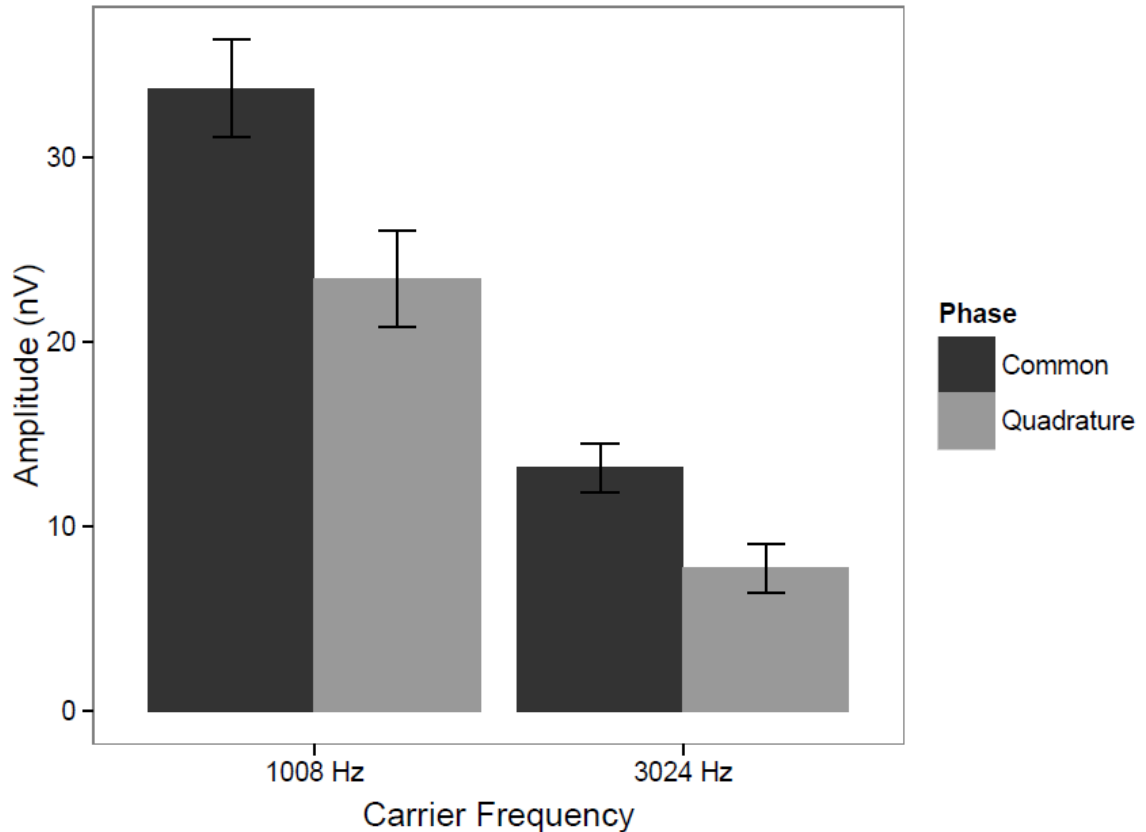
Figure 12. Envelope following response amplitude at two carrier frequencies in both common and quadrature phase. Results were collapsed across modulation frequency (74 & 518 Hz). Ten individuals with normal hearing were included in this data.

3.4.3 Discussion

Based on this experiment we have evidence that some of the EFR response at each carrier frequency can be attributed to interactions on the basilar membrane, as is commonly thought, but only for the unresolved components (i.e. the 74 Hz modulator). Quadrature phase did not cause a significant decrease in response amplitudes (in comparison to common phase) for the resolved components, indicating that these responses were not driven by cochlear interactions.

There is also ample evidence to support a central origin of the EFR in this data. The simple fact that EFR were measured for very well resolved stimuli that should not interact on the basilar membrane supports this claim. It should be noted that responses are generally smaller to resolved harmonics (8.6-3.4 nanovolts for the grand average response to stimuli in common phase) than to unresolved harmonics (48.4-21.87 nanovolts for the grand average response to stimuli in common phase). This is expected based on the well-known decrease in EFR amplitude with increasing modulation frequency. Resolved responses were recorded at a much higher frequency (518 Hz) than unresolved responses (74 Hz). It is also possible that unresolved responses have contributions from both cochlear and post-synaptic origins, making them larger. The finding that EFR for resolved stimuli were not significantly impacted by quadrature phase also supports the central origin hypothesis as does the seeming dependency on component frequencies being within the range of phase locking in the auditory nerve.

3.5 Experiment 3b- Bundled phase manipulation

3.5.1 Rationale

We investigated whether the response to combinations of two SAM tones presented together is representative of the response of individual SAM tones measured in Experiment 3a. This experiment was conducted to explore whether the same information gathered in the previous experiment could be gathered accurately in half the time.

3.5.2 Results

Repeated measures ANOVA found no significant effect of grouping of stimuli (single or pairs of SAM tones; $p=0.09$) and no significant interaction effects with carrier frequency ($p=0.29$), modulation frequency ($p=0.16$), or phase ($p=0.12$).

3.5.3 Discussion

It is common practice to use many carrier and modulation frequencies simultaneously when measuring the FFR and EFR in the ASSR response. Measuring

bundles of responses concurrently saves a lot of clinical time and allows for more repetition of responses. This experiment supports the notion that you can simultaneously measure both the response to a resolved and unresolved stimulus and, based on our previous support of two origins of the EFR response, can therefore investigate an individual's encoding of both in less time.

CHAPTER 4   GENERAL DISCUSSION

The results discussed above lend support to the hypothesis of two distinct origins of the EFR and suggest that the dominant mechanism depends primarily on the resolution of the stimulus components on the basilar membrane. As we hypothesized, Experiment 1 showed that as the stimulus pairs increased in frequency, while the f_0 was held constant, a U shaped function was found. The two distinct trends suggest that two different mechanisms are introducing the EFR. The accepted cochlear mechanism only makes logical sense when the stimulus components are unresolved and can therefore explain the rise in response amplitude as resolution decreases (Exp 1a). The suggestion that resolution plays a large role in the introduction of these responses is further demonstrated by the fact that when stimuli of similar component frequencies were made resolved the responses diminished considerably (Exp 1b). Even larger responses were recorded to resolved stimuli, a fact that does not fit into the cochlear model whatsoever (Exp 1a). We further investigated Laroche and colleagues' model (2013) that these responses arose centrally by observing the effects of phase locking limits on the amplitude of resolved responses; individual frequency components must be encoded in the auditory nerve before central interaction could occur (Exp 1b). Responses to stimuli of equal f_0 and equal resolution show a sloping decline as the component frequencies reach the limits of auditory nerve phase locking abilities, supporting our hypothesis that these resolved responses occur central to the auditory nerve (Exp 1a & 1b). Experiment 3 lent further support to our two mechanism model by demonstrating that unresolved components were critical when a high frequency carrier was used and that when the periodicity envelope was dampened in the stimulus these responses were largely diminished. Low-frequency carriers, however, showed robust responses whether the components were resolved or unresolved, though the unresolved were more affected by quadrature phase. As suggested by Laroche and colleagues (2013) this two mechanism model is consistent with our knowledge of filter bandwidth changes in the cochlea and phase locking limitations in the auditory system.

There is other evidence which suggests that f_0 information for resolved and unresolved components may arise from different auditory processes. In the pitch literature, resolved harmonics are often reported as having a stronger sensation of pitch and a lower discrimination threshold than unresolved harmonics (Krishnan & Plack, 2011). Carlyon & Shakleton (1994) found that subjects were better able to compare the pitches of two unresolved or two resolved stimuli than compare resolved with unresolved stimuli. Even when trained to differentiate between harmonics, those asked to distinguish between groups of resolved harmonics improved over time (unlike those differentiating unresolved harmonics) but their skills did not transfer to unresolved harmonics (Grimault, Micheyl, Carlyon, & Collet, 2002). Laroche *et al*. (2013) also found that discrimination of unresolved harmonics is more affected by noise than resolved components while White and Plack (1998) discovered that integration time (or duration of stimulus presentation) for f_0 discrimination of resolved harmonics is shorter than for unresolved harmonics. It is not only discrimination ability that is affected by the resolution of stimulus components, however. Krishnan & Plack (2011) found stronger EFR responses to resolved stimuli than unresolved stimuli, just as we did in the present study. The fact that unresolved and resolved harmonics have so many different perceptual characteristics suggests that they are treated differently by the auditory system. It then follows that extraction of the periodicity envelope could occur by different mechanisms depending on resolution as well.

The accepted model of cochlear interaction giving rise to the EFR for unresolved harmonics is supported by this study as well as the ASSR literature. It is believed that energy at the periodicity envelope is introduced due to cochlear non-linearity, including both compression and rectification, because both the modulation frequency and the component frequencies can be seen in primary auditory nerve fiber discharge (Picton *et al.,* 2003a; Khanna & Teich, 1989). It is the interaction between the travelling waves on the basilar membrane that begins the distortion process. Khanna (2002) measured this non-linearity at the level of the Hensen cells in living guinea pigs. He found that mechanical vibrations on the basilar membrane contained not only the original stimulus

frequencies but their modulation frequency as well. From this he postulated that the non-linearity present at this early stage in cochlear transduction is likely linked to outer hair cell movement and that one of the main functions of non-linearity at this level is to demodulate incoming signals. For non-linearity to introduce energy at the modulation frequency, however, stimulus travelling waves should be close enough on the basilar membrane to mechanically stimulate the same population of inner hair cells, indicating that at least two components of a stimulus should be unresolved (Greenberg *et al.* 1987). Auditory Steady State Responses performed clinically are done using mostly unresolved components, suggesting that in addition to estimating hearing thresholds this measure indicates the health of the cochlear transduction process (Korczak *et al.,* 2012).

The ability of resolved stimulus FFR components to interact beyond the cochlea as we propose depends on two main factors: robust phase locking in the auditory nerve as well as widening tonotopic filters due to converging inputs in the central nervous system (i.e. in the cochlear nucleus). It is generally believed that as the auditory neuroaxis is ascended beyond the auditory nerve the limits of phase locking decrease and the auditory filters widen. The carrier frequency used to evoke the EFR must therefore be minimally within the phase locking limits of the auditory nerve: without temporal encoding of the original stimulus components in the periphery it is obviously impossible for them to temporally interact centrally. Near field recordings in the auditory nerves of cats have found phase locking limits ranging from 2000 Hz (Tasaki, 1954) to 4-5000 Hz (Joris & Verschooten, 2013). Rose *et al*. (1967) concluded that in a squirrel monkey's auditory nerve fiber tuned to 4000 Hz, phase locking was best below 2000 Hz then gradually decreased until the upper limit of 5000 Hz was reached. Our findings align with these results since we saw EFR responses to resolved stimuli of 3024 Hz, suggesting that the individual components could be phase locked at this high frequency level, and that the strongest responses seen were to lower frequency components (low harmonics in Experiments 1 and 2 and the lower carrier frequency in Experiment 3). Since the limits of phase locking decrease with each subsequent auditory nucleus (AN <5000 Hz, SOC <3000 Hz, auditory cortex < 250 Hz; Joris & Verschooten, 2013) the highest stimulus

frequency that could still generate an EFR response may give us insight into where this interaction occurs along the neuroaxis. The very principle that allows these individual components to interact in the cochlea, or beyond, is that at the point of interaction they must be found within the same tonotopic filter. In the IC, for example, tuning is broader, with inputs from many auditory nerve fibers, so that components that were very well resolved in the cochlea would be unresolved in the upper brainstem (Langner, 1992). What we understand, therefore, about phase locking and auditory filters fit into our proposed model of central interaction creating energy at the periodicity envelope, as measured in the EFR.

Through this discussion we have established that it is conceptually possible for distinct tones to interact centrally to create energy at the f_0, but is there any non-refutable evidence that it can actually occur? It does indeed, as is elegantly shown by the existence of binaural beats. A perception of a tone waxing and waning in amplitude is achieved when two pure tones close in frequency are delivered dichotically, one to each ear. This beating sensation could only occur if the individual tones were carried by synchronous nerve impulses until they are able to interact at or medial to the superior olivary complex (Oster, 1973; Stewart, 1917). Of course the perception of a binaural beat might reflect rate coding related to the synchronous activity from each ear, but there is electrophysiological evidence for temporal coding of the beat frequency. Vernon, Peryer, Louch, & Shaw (2014) found evidence of temporal binaural beat activity for low frequency carriers (200-900 Hz) and low modulation frequencies (2-30 Hz). This suggests two things: that phase locking to the components is likely needed and that the two frequencies must be within an auditory filter at that level of the brainstem. Arnold and Burkard (2000) also found energy at the modulation frequency in the inferior colliculus of cat to dichotically presented tones of 2000 and 2100 Hz. These findings fit with our proposal that resolved, low frequency, harmonics must first be encoded before they can interact centrally to create a periodicity envelope. Bernstein & Oxenham (2003) furthered this discussion by presenting odd harmonics into one ear and even harmonics to the other, making them resolved regardless of carrier frequency, and asking participants

to discriminate between the dichotically presented stimuli and a pure tone based on pitch. They found that individuals were equally able to discriminate between lower frequency harmonics (usually resolved in the cochlea) and between higher frequency harmonics (usually unresolved in the cochlea). This illustrates three important concepts: that individual components can interact centrally to create an f_0, as is seen in the binaural beats literature, that periodicity envelope information converges from unresolved and resolved components somewhere in the central auditory nervous system as Laroche *et al.* (2013) suggested, and that there is something about the divergent processing of unresolved and resolved components before this central nucleus that makes one more perceptually salient in the pitch discrimination literature.

Where along the post-synaptic pathway the periodicity envelope arises to resolved harmonics, however, is still unknown. It is plausible that the periodicity envelope may be introduced in the cochlear nucleus (CN) with the proximal source of the scalp-recorded activity coming from the upper brainstem. The cochlear nucleus is known to faithfully transmit periodicity envelope information with little distortion but there is also evidence that it enhances modulation amplitude (Møller 1972; Bahmer & Langner, 2006). Møller (1972) found an increase of modulation depth of 40% (from 10%-50%) in some CN chopper cells in the rat. Known as 'intrinsic oscillators' chopper cells in the CN fire at regular intervals (modulation frequency and integer multiples) for the duration of the stimulus. Also, different populations of chopper cells have different modulation frequencies to which they optimally fire, creating a type of modulation filterbank (Joris *et al*. 2004). Being able to faithfully represent a modulation frequency up to 500-700 Hz, this nucleus would likely be able to encode components that were comfortably resolved in the cochlea (Langner, 1992). Laroche *et al*. (2013) also suggested that a non-linear interaction occurs between resolved and unresolved components in the upper brainstem because the response amplitude of each of the individual formant harmonics added together was larger than all of the components recorded concurrently, as was seen in this study.

47

There were, however, some limitations in our study. It could be argued that the responses we were measuring to resolved harmonics were actually responses to travelling waves interacting at the base of the cochlea, where they would be unresolved. Although masking would seem to put this issue to rest, so little is known about the effects of masking at the site of central EFR introduction that its use drew up more far-reaching questions than it answered in the piloting phase. The fact that responses to low-frequency resolved stimuli were significantly larger than those to the unresolved high frequency stimuli seems to refute the idea that the EFR is introduced purely in the cochlea. If resolved responses were indeed being introduced at the base of the cochlea where they are unresolved they should be miniscule since the tail of the travelling wave would be small at such a far-off cochlear location at a 70 dB SPL presentation level. Another limitation of our study was the smaller growth on the unresolved side of the U function. It is possible that response amplitudes would have grown larger if more unresolved stimuli were employed: the limitation in this regard was overall recording time.

Although most of our data showed straightforward trends and fit within our understanding of the auditory system and its workings there were a few anomalies that are difficult to explain. The most evident is the lack of a U shaped trend, or any overall trend, in the decreasing but not the increasing bundled data of Experiment 2. The decreasing bundle had more resolved low-frequency stimuli and more unresolved high frequency stimuli than the increasing bundle, suggesting that responses should be more robust in this condition. It is possible that cochlear two-tone suppression caused alterations in the encoding of f_0, but this only explains the unexpected results in the unresolved conditions. Even though the increasing bundle does show a general U shape, as we would predict, there is a slight rise in response amplitude in the 1308-1780 Hz range which we are unable to explain.

If there are two distinct origins of the periodicity envelope as has been suggested, it could have a profound impact on our understanding of the potential value of the EFR. In its most common clinical use, ASSR to unresolved harmonics are measured to assess hearing thresholds in difficult-to-test patients (Korczak *et al*, 2012). It is very important

that we understand where any electrophysiological response is introduced, how it is propagated and measured at the source, to properly interpret findings made in a clinical or research setting. Using unresolved stimuli in ASSR measurement may give a good estimation of cochlear health and hearing threshold but tells us nothing of an individual's ability to phase lock to temporal fine structure or to extract modulation information when the stimulus components are resolved. The EFR with a range of resolved and unresolved stimuli (as was used in Experiment 1a) could be used to assess individuals' phase locking abilities (e.g., by recording the EFR as a function of carrier frequency for resolved harmonics) and cochlear filter widths. If an individual had lower than average phase locking abilities, for example, we would expect that their responses to resolved harmonics with increasing frequency would deteriorate more quickly than we measured in Experiment 1a. With a similar reasoning, if an individual had wider than average cochlear filters we would expect responses to increase much more quickly as the components become unresolved. With further investigation, an ASSR to resolved harmonics may also be diagnostically useful to assess individuals with temporal processing difficulties or troubles in background noise since the low-frequency resolved components are believed to be linked to speech in noise abilities (Young, 2008; Laroche *et al.* 2013). The EFR could then be used for threshold and supra-threshold testing in a variety of patients of all ages.

Future studies investigating the EFR should consider the possibility of two sites of response introduction depending on the resolvability of the components. Although responses to unresolved harmonics have dominated in the literature due to their use in threshold estimation, responses to resolved harmonics may potentially provide clinically useful information as well. Further research is needed to support the claim that the EFR can arise centrally, both in human and animal models, and to investigate where along the auditory pathway it is introduced. It would also be clinically useful to determine if the EFR could be used to identify individuals with degraded phase locking or widened cochlear filters. Finally, the problem of speech in noise difficulties is very pervasive amongst senior citizens, even with normal hearing. It has been suggested that degradation

of envelope encoding may predict speech in noise difficulties and should be investigated further.

CHAPTER 5   CONCLUSIONS

The results of this study support the hypothesis made by Laroche *et al.* (2013) that periodicity envelope energy is introduced both peripherally and centrally. A U shaped function was found with pairs of harmonics of 215 Hz of increasing frequency, suggesting that a different mechanism is responsible for the decline in response amplitude of low frequency resolved harmonics and the rise in response amplitude for high frequency unresolved harmonics. Responses to resolved harmonics were found to be larger, in general, than those to unresolved harmonics, less susceptible to quadrature phase, and to adhere to the phase locking limits of the auditory nerve (even when stimuli were equally resolved across the tested frequencies). These findings suggest that not only do the resolved responses not come from interactions in the unresolved cochlear base but that they are introduced centrally. Where the EFR is introduced along the central auditory pathway and what this measured response can tell us about an individual's phase locking ability, cochlear filter width, or ability to hear in background noise remains for further investigation. Nevertheless, the growing evidence suggesting that the periodicity envelope arises at more than one location along the neuroaxis adds to our understanding of the complexity of the auditory system and its processes.

REFERENCES

Aiken, S.J. & Picton, T.W. (2008). Envelope and spectral frequency-following responses to vowel sounds. *Hearing Research,* 245, 35-47.

Arnold, S., & Burkard, R. (2000). Studies of interaural attenuation to investigate the validity of a dichotic difference tone response recorded from the inferior colliculus in the chinchilla. *Journal of the Acoustical Society of America,* 107(3), 1541-1547.

Bahmer, A., & Langner, G. (2006). Oscillating neurons in the cochlear nucleus: I. Experimental basis of a simulation paradigm. *Biological Cybernetics*, 95, 371-379.

Baker, R.J., & Rosen, S. (2006). Auditory filter nonlinearity across frequency using simultaneous notched-noise masking. *Journal of the Acoustical Society of America,* 119(1), 454-462.

Bernstein, J.G., & Oxenham, A.J. (2003). Pitch discrimination of diotic and dichotic tone complexes: Harmonic resolvability or harmonic number? *Journal of the Acoustical Society of America,* 113(6), 3323-3334.

Burkard, R.F., Eggermont, J.J., & Don, M. (2007). Auditory Evoked Potentials: Basic Principles and Clinical Application. Philadelphia : Lippincott Williams & Wilkins.

Carlyon, R.P., & Shackleton, T.M. (1994). Comparing the fundamental frequencies of resolved and unresolved harmonics: Evidence for two pitch mechanisms? *Journal of the Acoustical Society of America,* 95(6), 3541-3554.

Cordon, C.J., White, K.R., & Feng, A.S. (1996). Neurons with different temporal firing patterns in the inferior colliculus of the little brown bat differentially process sinusoidal amplitude-modulated signals. *Journal of Comparative Physiology A,* 178(2), 147-157.

Fletcher, H. (1940). Auditory patterns. *Reviews of Modern Physics,* 12, 47-65.

Frisina, R.D., Smith, R.L., & Chamberlain, S.C. (1985). Differential encoding of rapid changes in sound amplitude by second-order auditory neurons. *Experimental Brain Research*, 60(2), 417-422.

Frisina, R.D., Smith, R.L., & Chamberlain, S.C. (1990). Encoding of amplitude modulation in the gerbil cochlear nucleus: I. A hierarchy of enhancement. *Hearing Research,* 44, 99-122.

Gelfand, S. A. (2010). Cochlear Mechanisms and Processes. In Hearing: *An Introduction to Psychological and Physiological Acoustics* (pp. 72-102). London, UK: Informa Healthcare Ltd.

Goldberg, J.M. & Brown, P.B. (1969). Response of binaural neurons of dog superior olivary complex to dichotic tonal stimuli: Some physiological mechanisms of sound localization. *Journal of Neurophysiology*, 32(4), 613-36.

Greenberg, S., Marsh, J.T., Brown, W.S., & Smith, J.C. (1987). Neural temporal encoding of low pitch. I. Human frequency-following response to complex tones. *Hearing Research,* 25, 91-114.

Grimault, N., Micheyl, C., Carlyon, R.P., & Collet, L. (2002). Evidence for two pitch encoding mechanisms using a selective auditory training paradigm. *Perception & Psychophysics*, 64 (2), 189-197.

Harada, J., Aoyagi, M., Suzuki, T., Kiren, T., & Koike, Y. (1994). A study on the phase spectral analysis of middle latency response and 40-Hz event-related potential in central nervous system disorders. *Acta Oto-laryngologica Supplement,* 511, 34-39.

Hari, R., Hamalainen, M., & Joutsiniemi, S.L. (1989). Neuromagnetic steady-state responses to auditory stimuli. *Journal of the Acoustical Society of America,* 86(3), 1033-1039.

Hartmann, W.M. (1997). *Signals, Sound, and Sensation.* American Institute of Physics : New York : Springer Publishing Ltd.

Henning, G.B. (1974). Detectability of interaural delay in high-frequency complex waveforms. *Journal of the Acoustical Society of America,* 55(1), 84-90.

Herdman, A.T., Lins, O., Van Roon, P., Stapells, D.R., Scherg, M., & Picton, T.W. (2002). Intracerebral sources of human Auditory Steady-State Responses. *Brain Topography,* 15(2), 69-86.

Hewitt, M.J. & Meddis, R. (1994). A computer model of amplitude-modulation sensitivity of single units in the inferior colliculus. *Journal of the Acoustical Society of America*, 95(4), 2145-2159.

Javel, E. (1980). Coding of AM tones in the chinchilla auditory nerve: Implications for the pitch of complex tones. *Journal of the Acoustical Society of America*, 68(1), 133-146.

Joris, P.X., Schreiner, C.E. & Rees, A. (2004). Neural processing of amplitude-modulated sounds. *Physiological Reviews*, 84(2), 541-547.

Joris, P.X. & Verschooten, E. (2013). On the limit of neural phase locking to fine structure in humans. *Advances in Experimental Medicine and Biology*, 787, 101-108.

Joris, P.X., & Yin, T.C.T. (1992). Responses to amplitude-modulated tones in the auditory nerve of the cat. *Journal of the Acoustical Society of America*, 91(1), 215-232.

Khanna, S.M. (2002). Non-linear response to amplitude-modulated waves in the apical turn of the guinea pig cochlea. *Hearing Research,* 174, 107-123.

Khanna, S.M., Teich, M.C. (1989). Spectral characteristics of the responses of primary auditory-nerve fibers to amplitude-modulated signals. *Hearing Research,* 39, 143-158.

Kim, D.O., Sirianni, J.G., & Chang, S.O. (1990). Responses of DCN-PVCN neurons and auditory nerve fibers in unanesthetized decerebrate cats to AM and pure tones: Analysis with autocorrelation/ power- spectrum. *Hearing Research,* 45, 95-113.

Korczak, P., Smart, J., Delgado, R., Strobel, T.M., & Bradford, C. (2012). Auditory steady-state responses. *Journal of the American Academy of Audiology*, 23, 146-170.

Krishna, B.S., & Semple, M.N. (2000). Auditory temporal processing: Responses to sinusoidally amplitude-modulated tones in the inferior colliculus. *Journal of Neurophysiology,* 84, 255-273.

Krishnan, A., & Plack, C.J. (2011). Neural encoding in the human brainstem relevant to the pitch of complex tones. *Hearing Research*, 275, 110-119.

Langner, G. (1992). Review article: Periodicity coding in the auditory system. *Hearing Research,* 30, 115-142.

Langner, G. & Schreiner, C.E. (1988). Periodicity coding in the inferior colliculus of the cat. I. Neuronal mechanisms. *Journal of Neurophysiology,* 60(6),1799-1822.

Laroche, M., Dajani, H.R., Prévost, F., & Marcoux, A.M. (2013). Brainstem auditory responses to resolved and unresolved harmonics of a synthetic vowel in quiet and noise. *Ear and Hearing,* 34(1), 63-74.

Lins, O.G., Picton, P.E., & Picton, T.W. (1995). Auditory steady-state responses to tones amplitude-modulated at 80-110 Hz. *Journal of the Acoustical Society of America*, 97(5), 3051-3063.

McFadden, D. (1988). Failure of a missing-fundamental complex to interact with masked and unmasked pure tones at its fundamental frequency. *Hearing Research,* 32, 23-40.

Micheyl, C., & Oxenham, A.J. (2004). Sequential f_0 comparisons between resolved and unresolved harmonics: No evidence for translation noise between two pitch mechanisms. *Journal of the Acoustical Society of America,* 116(5), 3038-3050.

Møller, A.R. (1972). Coding of amplitude and frequency modulated sounds in the cochlear nucleus of the rat. *Acta Physiologica Scandinavica*, 86, 223-238.

Moore, B.J.C. (2008). The role of temporal fine structure processing in pitch perception, masking, and speech perception for normal-hearing and hearing-impaired people. *Journal of the Association for Research in Otolarnygology,* 9, 399-406.

Moore, B.J.C., & Glasberg, B.R. (1983). Suggested formulae for calculating auditory-filter bandwidths and excitation patterns. *Journal of the Acoustical Society of America,* 74(3), 750-753.

Nuttall, A.L. & Dolan, D.F. (1996). Steady-state sinusoidal velocity responses of the basilar membrane in guinea pig. *Journal of the Acoustical Society of America*, 99(3), 1556-1565.

Oster, G. (1973). Auditory beats in the brain. *Scientific American,* 229(4), 94-102.

Perrott, D.R., & Nelson, M.A. (1969). Limits for the detection of binaural beats. *Journal of the Acoustical Society of America*, 46(6), 1477-1481.

Picton, T.W. (2001). *Human Auditory Evoked Potentials*. San Diego: Plural Publishing.

Picton, T. W. (2013). Hearing in time: Evoked potential studies of temporal processing. *Ear and Hearing,* 34(4), 385-401.

Picton, T.W., Dimitrijevic, A., & John, M.S. (2002). Multiple auditory steady-state responses. *The Annals of Otology, Rhinology & Laryngology*, 111(5), 16-21.

Picton, T.W., Dimitrijevic, A., Perez-Abalo, M.C., & Van Roon, P. (2005). Estimating audiometric thresholds using auditory steady-state responses. *Journal of the American Academy of Audiology,* 16, 140-156.

Picton, T.W., John, M.S., Dimitrijevic, A., & Purcell, D. (2003a). Human auditory steady-state responses. *International Journal of Audiology,* 42, 177-219.

Picton, T. W., John, M.S., Purcell, D.W., & Plourde, G. (2003b). Human auditory steady-state responses: the effects of recording technique and state of arousal. *Anesthesia and Analgesia*, 97(5), 1396- 1402.

Preuss, A., & Müller-Preuss, P. (1990). Processing of amplitude modulated sounds in the medial geniculate body of squirrel monkeys. *Experimental Brain Research,* 79, 207-211.

Rance, G., & Rickards, F. (2002). Prediction of hearing threshold in infants using Auditory Steady-State Evoked Potentials. Journal of the American Academy of Audiology, 13, 236-245.

Rees, A., & Møller, A.R. (1987). Stimulus properties influencing the responses of inferior colliculus neurons to amplitude-modulated sounds. *Hearing Research,* 27(2), 129-143.

Rees, A., & Palmer, A.R. (1989). Neuronal responses to amplitude-modulated and pure-tone stimuli in the guinea pig inferior colliculus, and their modification by broadband noise. *Journal of the Acoustical Society of America*, 85(5), 1978-1994.

Rhode, W.S., & Greenberg, S. (1994). Encoding of amplitude modulation in the cochlear nucleus of the cat. *Journal of Neurophysiology,* 71(5), 1797-1825.

Rose, J.E., Brugge, J.F., Anderson, D.J., & Hind, J.E. (1967). Phase-locked responses to low-frequency tones in single auditory nerve fibers of the squirrel monkey. *Journal of Neurophysiology,* 30(4), 769-793.

Rosen, S. (1992). Temporal information in speech: Acoustic, auditory and linguistic aspects. *Philosophical Transactions: Biological Sciences*, 336 (1278), 367-373.

Rouiller, E., De Ribaupierre, Y., Toros-Morel, A., & De Ribeaupierre, F. (1981). Neural coding of repetitive clicks in the medial geniculate body of cat. *Hearing Research,* 5, 81-100.

Scharf, B. (1961). Complex sounds and critical bands. *Psychological Bulletin,* 58(3), 205-217.

Schreiner. C.E. & Langner, G. (1988). Periodicity coding in the inferior colliculus of the cat. II. Topographical organization. *Journal of Neurophysiology,* 60(6), 1823-1840.

Stewart, G.W. (1917). Binaural beats. *Physical Review,* 9(6), 502-508.

Tasaki, I. (1954). Nerve impulses in individual auditory nerve fibers of guinea pig. *Journal of Neurophysiology,* 17(2), 97-122.

Vernon, D., Peryer, G., Louch, J., & Shaw, M. (2014). Tracking EEG changes in response to alpha and beta binaural beats. *International Journal of Psychophysiology*, 93, 134-139.

Wang, X., & Sachs, M.B. (1993). Neural encoding of single-formant stimuli in the cat. I. Responses of auditory nerve fibers. *Journal of Neurophysiology*, 70(3), 1054-1075.

White, L.J., & Plack, C.J. (1998). Temporal processing of the pitch of complex tones. *Journal of the Acoustical Society of America*, 103(4), 2051-2063.

Young, E.D. (2008). Neural representation of spectral and temporal information in speech. *Philosophical Transactions of the Royal Society B*, 363, 923-945.