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Characterization of Auditory Evoked Potentials From Transient Binaural beats Generated by Frequency Modulating Sound Stimuli

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CHARACTERIZATION OF AUDITORY EVOKED POTENTIALS FROM TRANSIENT BINAURAL BEATS GENERATED BY FREQUENCY MODULATING SOUND STIMULI

By

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When two pure-tone (2T) stimuli with slightly different frequencies are presented independently to each ear, an auditory illusion, called binaural beats (BB), is perceived as a faint pulsation over a single tone. The frequency of the perceived tone is equal to the mean frequency of 2T and the pulsation has a rate equal to the difference of the two.

The interaction of the 2T stimuli, inside the auditory cortex, can be recorded in the form of auditory steady state responses (ASSR) using conventional electroencephalography (EEG) or magnetoencephalography (MEG). The recorded ASSR usually have small amplitudes and require additional signal processing to separate them from the surrounding cortical activity. The transient auditory evoked potentials (AEPs) may provide more information about the physiology behind the generation of the BBs. Currently most methods can only generate transient AEPs to binaural phase disparities in random noise, or use amplitude modulating (AM) tones to trigger a binaural frequency difference (BFD).

For this dissertation, a method was developed which uses two frequency modulating (FM) sounds to generate an instantaneous BFD which only lasts for the duration of a single or unitary beat. One major advantage of this method is that it

separates the beating rate from the BFD allowing for independent control of the beat occurrences.

This dissertation provides an in depth description of the stimulus generation and acquisition methodology used to evoke transient AEPs to unitary BBs. Several studies were designed to characterize the behavior of the AEPs to some of the key stimulus parameters design and to obtain an optimal set of parameter values that can be used to generate robust transient AEPs.

The result was a method that can be used to generate unitary BBs that have equivalent characteristics to the BBs generated using the 2T method. Furthermore the studies showed that the method is capable of generating BBs that evoke repeatable and robust transient AEPs with large amplitudes and late latencies.

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LIST OF ABBREVIATIONS

2T	Two tone
ABR	Auditory Brainstem Responses
AEP	Auditory Evoked Responses
AM	Amplitude Modulation
ANOVA	Analysis of Variance
AP	Action Potential
ASSR	Auditory Steady State Responses
AVCN	Anterior Ventral Cochlear Nucleus
AVCN-A	Anterior Ventral Nucleus - Anterior portion
AVCN-P	Anterior Ventral Nucleus - Posterior portion
BB	Binaural Beat
BBR	Binaural Beat Responses
BCR	Binaural Compound Responses
BFD	Binaural Frequency Difference
BM	Basilar Membrane
BOI	Beat Onset Interval
CLAD	Continuous Loop Averaging Deconvolution
DNLL	Dorsal Nucleus of the Lateral Lemniscus
EEG	Electroencephalography
FFR	Frequency Following Responses
FM	Frequency Modulation
FMR	Frequency Modulation Responses
$\mathbf{FM_{R\uparrow L\downarrow}}$	Binaural dichotic stimulation using FM stimuli
$\mathbf{FM_{R\downarrow L\downarrow}}$	Binaural diotic stimulation using FM stimuli
GUI	Graphical User Interface
IBI	Inter Beat Interval
IC	Inferior Colliculus
IPD	Interaural Phase Difference
ISI	Inter Stimulus Interval
ITD	Interaural Time Disparities
LE	Left Ear
LL	Lateral Lemniscus
LLR	Late Latency Responses
LNTB	Lateral Nucleus of the Trapezoid Body
LSO	Lateral Superior Olive
MEG	Magneto encephalography
MGB	Medial Geniculate Body
MLR	Middle Latency Responses
MNTB	Medial Nucleus of the Trapezoid Body

MSO	Medial Superior Olive
RE	Right Ear
SBB	Subjective Binaural Beats
SLR	Short Latency Responses
SOA	Stimulus Onset Asynchrony
SOC	Superior Olivary Complex
VCN	Ventral Cochlear Nucleus

Chapter 1.
BACKGROUND

1.1 Introduction

When two sounds with slightly different frequencies, f_1 and f_2, (shown in the top plot of Figure 1-1) interfere with each other the result is a new sound with a single frequency tone with sinusoid amplitude modulation (AM) (shown in the bottom plot of Figure 1-1). The resultant interference is called acoustic beats and can be heard as a

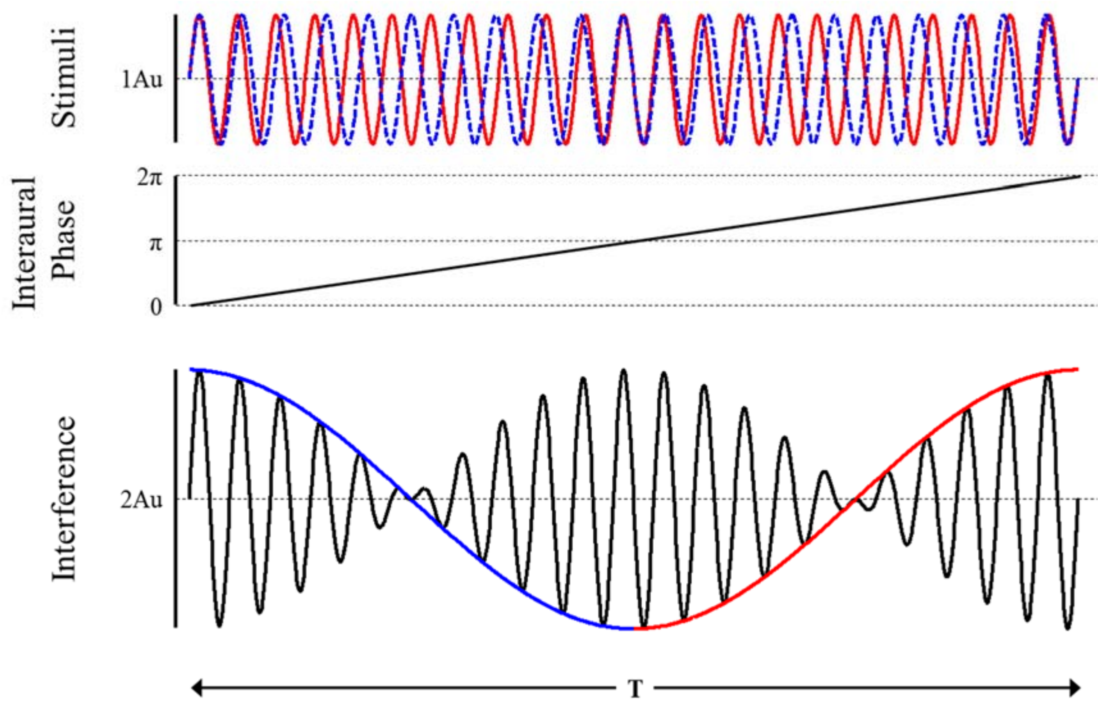

Figure 1-1 Interference of two arbitrary sinusoids with a frequency difference of 2Hz. The red-solid waveform has a frequency of 23 cycles in a period T while the left-dashed waveform has a frequency of 21 cycles in a period T. The middle plot shows the phase difference between the two waveforms. The bottom plot shows the interference of the two waveforms with a base frequency equal to the average of the two and the amplitude modulation (AM) with a frequency equal to half of the difference of the two. The AM waveform is superimposed on top of the interference.

pulsating tone with a base frequency equal to the mean of f_1 and f_2 and pulsation rate equal to the difference of the two. If the same two sounds are presented binaurally, simultaneously to both ears, but physically separate from each other, a pulsating sensation is still perceived, much like the acoustic beats. This effect is an auditory illusion in which the auditory system combines the two sounds internally thus resulting in the perception of pulsation and is known as binaural beats (BB) (Licklider et al. 1950, Perrott and Nelson 1969, Fritze 1985, Schwarz and Taylor 2005, Karino et al. 2006, Draganova et al. 2008, Pratt et al. 2009a, Pratt et al. 2010, Grose and Mamo 2012).

The perception of BBs is completely subjective, since the two sounds do not interfere in any way. The sound fluctuations of BBs are generated by the auditory system and the brain. The generally accepted physiological explanation for BBs is based on the temporal localization centers in the auditory system. These centers are primarily used for the localization of sounds with low frequencies (<1500 Hz) on the horizontal plane by measuring the interaural phase and time differences.

The early BB research primarily focused on the subjective perception of the BBs and the psychophysics of this phenomenon. More recently, with the advancement of technology, research has turned towards the electrophysiology and the generation of BBs. The current electrophysiology research shows that BBs can be objectively recorded and are generated along the central auditory system and cortex.

1.2 Phase Coding

The primary task of the auditory system is to interpret the air vibrations from the surrounding environment into what is perceived as sound. Complex sounds can be represented as the sum of many individual sounds with distinct frequencies, phases, and amplitudes. Many sensory cells, neurons, ganglia, and centers of the auditory system work together to convert theses air vibrations into what the brain interprets as sound. The cochlea is the sensory organ in the auditory system that converts the three distinct components of sound, mentioned above, into electrical impulses or action potentials (AP). The cochlea acts as a mechanical filter that distributes the sound vibrations into distinct frequency regions on the basilar membrane (BM), this is also known as place coding (Békésy and Wever 1960). The BM is lined with sensory cells that pick up the mechanical vibrations and convert them into APs. The APs are then relayed into

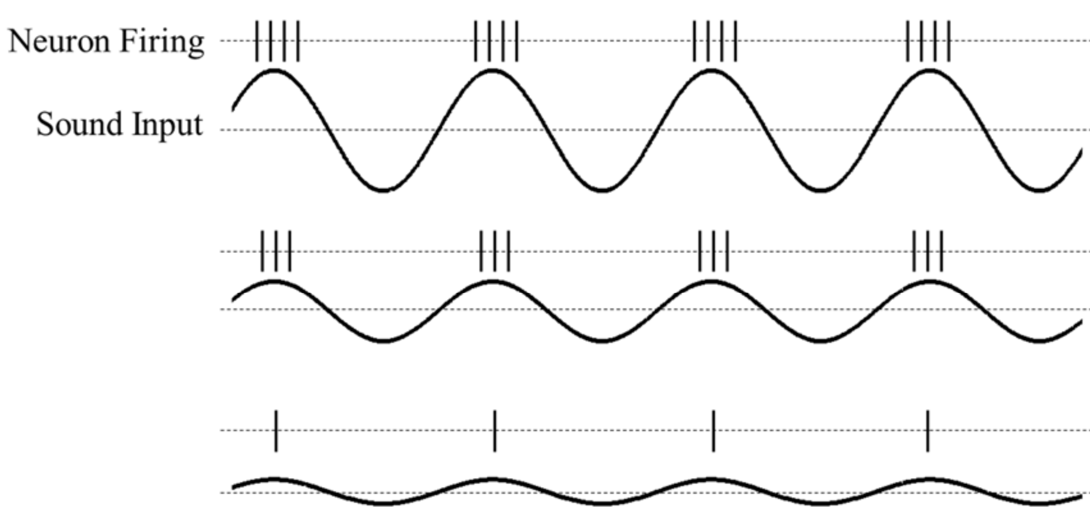

Figure 1-2 Simplified depiction of the phase coding that occurs in the cochlea. The intensity is coded as the density of the APs while the phase is coded as the gait of AP clusters. Not shown here, but the phase locking may not occur at the same point in the cycle for each frequency. As the intensity decreases the density of the APs reduces, while the phase information is still preserved.

frequency specific neurons of the auditory nerve (Cranial VIII). The rate of firing of individual neurons can be considered to be the primary mechanism of encoding sound information. Since each neuron is responsible for a distinct frequency, the amplitude of that frequency is coded by the firing rate of that particular neuron; louder sound will have faster firing rates and softer sound slower.

APs are elicited by unidirectional movements of the BM and the discharges occur within a specific time window, relative to the phase of a sinusoid (Palmer and Russell 1986). Figure 1-2 is a simplified representation of the phase-coding of a sinusoid sounds. The APs are clustered and locked to a single phase of the sinusoid. The intensity information is still conveyed as the density and the rate of firing in the phase-locked clusters. The phase-locking varies with the frequency and intensity of the sound (Picton 2011). The neural activity that is synchronized to a specific phase of a tone can be captured using scalp electrode in the form of frequency following responses (FFRs). Figure 1-3 shows that the amplitudes of the FFR change with respect to the frequency

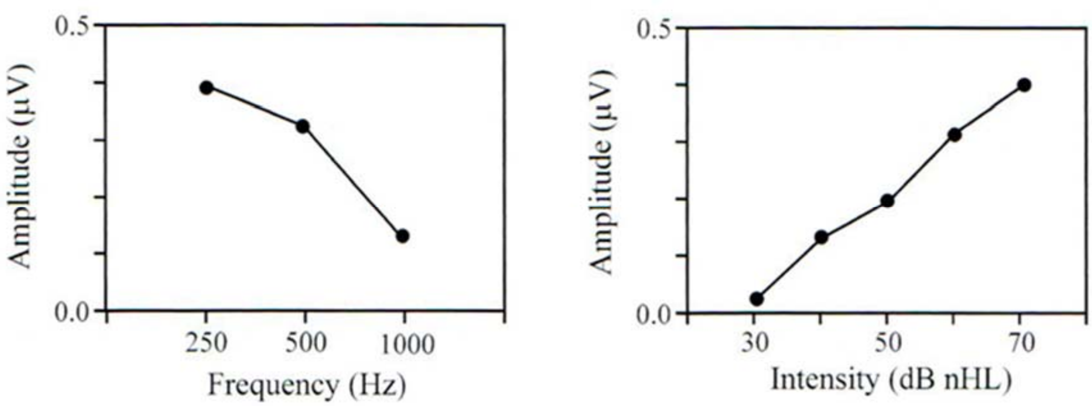

Figure 1-3 Characteristics of the FFR with respect to the stimulus frequency and intensity. The left plot shows the frequency characteristics of the amplitudes of FFRs with respect to the frequency of the tone delivered to the ear (at 60 dBHL). The right plot shows the amplitude response of the FFR to different stimulus intensities (at 500 Hz). Adapted from Picton 2011

and the intensity of the tone. The FFR reduce in amplitude as the frequency increases or as the intensity decreases. The upper limit for evoking FFRs is around 1500 to 2000Hz (Moushegian et al. 1973).

1.3 Binaural Pathways and Directional Hearing

Sound processing begins as early as the entry point to the brainstem. The ventral cochlear nuclei (VCN) are the entry points where the auditory nerves from both ears directly innervate the brainstem. The VCN contains several different kinds of specialized neurons that perform some of the initial signal processing and also act as a distribution center. This intricate distribution network continues in parallel pathways along the brainstem and midbrain until it reaches the auditory cortex in the brain. However, most of the binaural and interaural processing is performed in the superior olivary complex (SOC), more specifically the medial and lateral superior olive (MSO and LSO). The MSO and LSO are densely populated with low specific frequency neurons that are sensitive to small (microsecond) time and phase differences (Yin and Chan 1990).

The MSO is innervated by neurons projecting from the anterior portion of the anterior VCN (AVCN-A). The ipsilateral MSO directly receives inputs from the ipsilateral AVCN-A and from the contralateral AVCN-A via the trapezoid body (Harrison and Warr 1962). Both the ipsi and contralateral inputs are excitatory. In addition to the AVCN-A inputs the MSO is innervated by the ipsilateral medial nucleus of the trapezoid body (MNTB) and lateral nucleus of the trapezoid body (LNTB) (Saint Marie et al. 1989). Both of the AVCN-A are excitatory, while the MNTB is inhibitory

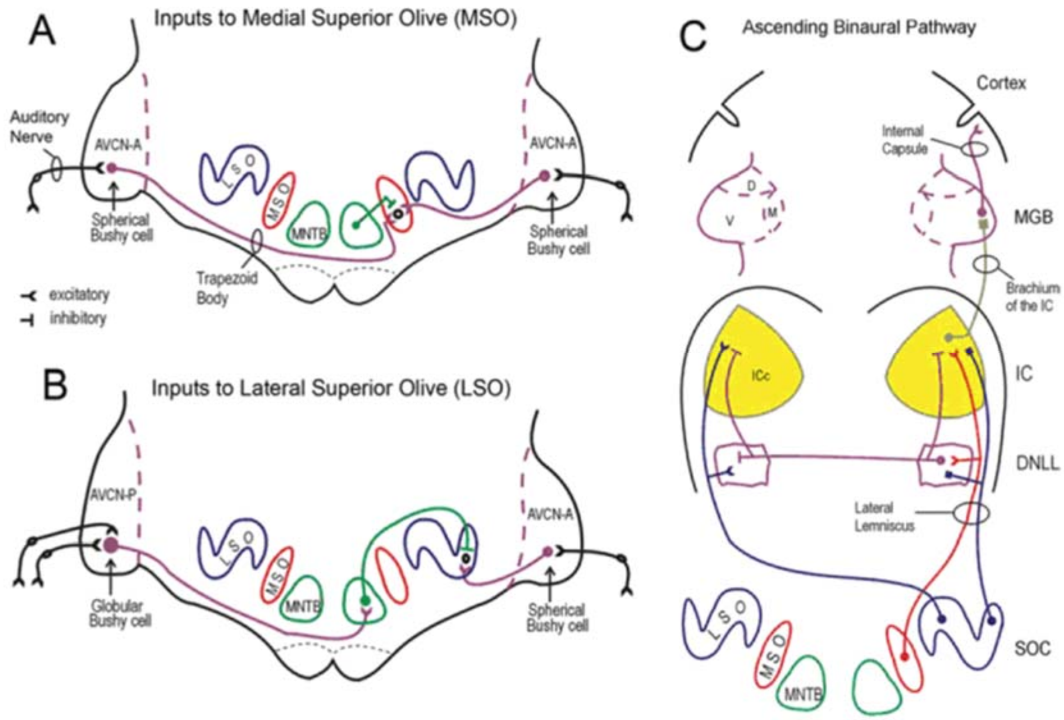

Figure 1-4 Binaural pathways from the cochlea to the auditory cortex. (A) The MSO innervated by excitatory projections from the ipsilateral and contralateral AVCN-A, and inhibitory projection from the MNTB. (B) The LSO innervated by the excitatory projections from the ipsilateral AVCN-A and inhibitory projections from the ipsilateral MNTB which in turn is innervated by the excitatory projections from the AVCN-P. (C) The DNLL innervations from the ipsilateral LSO and MSO and the contralateral DNLL and LSO. The IC innervated by the DNLL, LSO, and MSO. The projections from the IC innervate the MGB which then innervates the auditory cortex (Rees and Palmer 2010).

(Figure 1-4A). The cells inside the MSO act as coincidence detectors which fire maximally when APs from both AVCN-A inputs arrive at the same time. Furthermore the MSO is predominately innervated by low specific frequency neurons (Osen 1969).

The LSO similar to the MSO is innervated by the ipsilateral AVCN-A (Harrison and Warr 1962), but from the contralateral side it is innervated by the ipsilateral MNTB, which in turn is innervated by the posterior portion of the AVCN (AVCN-P). The AVCN-A input is excitatory while the MNTB input is inhibitory and the MNTB is innervated by an excitatory neuron from the AVCN-P (Figure 1-4B). Unlike the MSO the LSO is sensitive to interaural temporal variations of sound amplitudes for high frequencies (Joris and Yin 1995).

The binaural pathways continue (Figure 1-4) via the lateral lemniscus (LL) to the dorsal nucleus of the lateral lemniscus (DNLL). The ipsilateral LSO has projections to both the ipsilateral and contralateral DNLL, the only difference being that the contralateral projection is excitatory while the ipsilateral is inhibitory. The ipsilateral MSO, on the other hand, only has an excitatory projection to the ipsilateral DNLL. The DNLL then projects to the contralateral DDNL and the ipsilateral inferior colliculus (IC). In addition, to the DNLL projections the IC also has direct excitatory projections from the ipsilateral MSO, inhibitory projections from the ipsilateral LSO, and excitatory projections from contralateral LSO. Furthermore, the IC is innervated by the contralateral cochlear nucleus, contralateral IC, and the descending pathways from the primary auditory cortex. The IC then projects into the auditory thalamus, more specifically the medial geniculate body (MGB) which then projects to the primary auditory cortex (Rees and Palmer 2010).

1.4 Interaural Phase and Time Disparities

The auditory system is capable of localizing sound sources due to the fact that it has two ears and is capable of processing information from both simultaneously (binaurally). The azimuth angle of the sound source relative to the listener can be determined by two mechanisms. The first is the interaural level disparities (ILD), which occur due to masking by the head. The second are the interaural time disparities (ITD) that occur due to the distance which the sound needs to travel to each ear from a single source (Rayleigh 1907). ITDs can be classified into two categories: sustained and amplitude onset. Sustained ITDs occur when two identical sound stimuli with a slight phase delay are presented to each ear individually (Zwislocki and Feldman 1956). Amplitude onset ITDs occur during a slow onset of a high frequency (>1200Hz) sound.

The MSO is predominantly responsible for the processing of the sustained ITDs where the LSO is for the amplitude onset ITDs. The MSO contains specialized neurons which will achieve maximal firing rate if the APs from both ears arrive at the same time, resulting in a tuning curve-like behavior (Joris et al. 1998, Joris et al. 2006). Figure 1-5 shows the number of firings of a single coincidence detector neuron in the MSO as a function of ITD. The periodicity of the responses can be attributed to the pure-tone stimulation and the phase overlap at different phase delays (Yin and Chan 1990). The LSO is predominantly populated by high specific frequency neurons. Unlike the MSO, the LSO is more sensitive to the ITD of the onset of the stimulus rather than the phase (Joris et al. 1998, Joris et al. 2006). However, the MSO and LSO are only capable of detecting incidence of two APs, so the ITD and phase specificity are achieved by

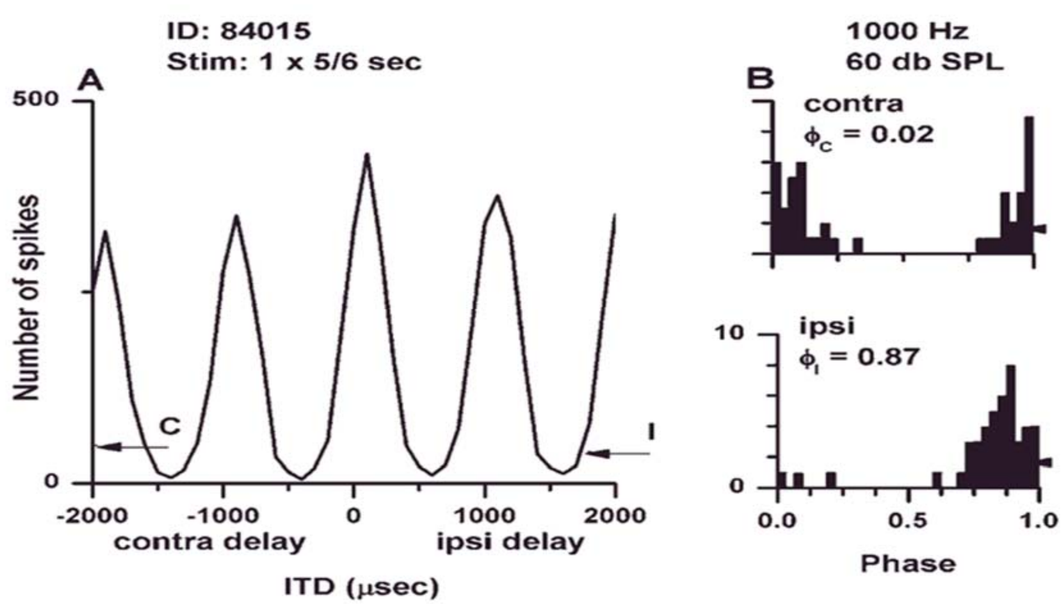

Figure 1-5 ITD tuning curve of an MSO neuron. (**A**) Number of APs with respect to ITD of an MSO neuron with maximum number of spikes at the specific ITD for that neuron and side peaks from the phase overall from the pure-tone stimulation. (**B**) Monaural firing histograms from ipsilateral and contralateral stimulation. (Yin and Chan 1990, Rees and Palmer 2010)

utilizing delay lines that rely on the propagation speed and time of an AP to travel along an axon (Figure 1-6) (Jeffress 1948). The delay lines determine the ITD specificity of the different regions of the MSO.

Further ITD processing occurs along the ascending pathways in the DNLL (Kuwada et al. 2006), IC (Kuwada et al. 1984), thalamus (Stanford et al. 1992), and the auditory cortex (Fitzpatrick et al. 2000, Ivarsson et al. 1988). The ITD specificity sharpens from the SOC to the thalamus and broadens from the thalamus to the auditory cortex (Yin and Kuwada 1983). This means the interaural time processing is a very complex process that takes place in several different nuclei in the brain stem and the cortex where it is finally translated into the azimuth angle of a sound source.

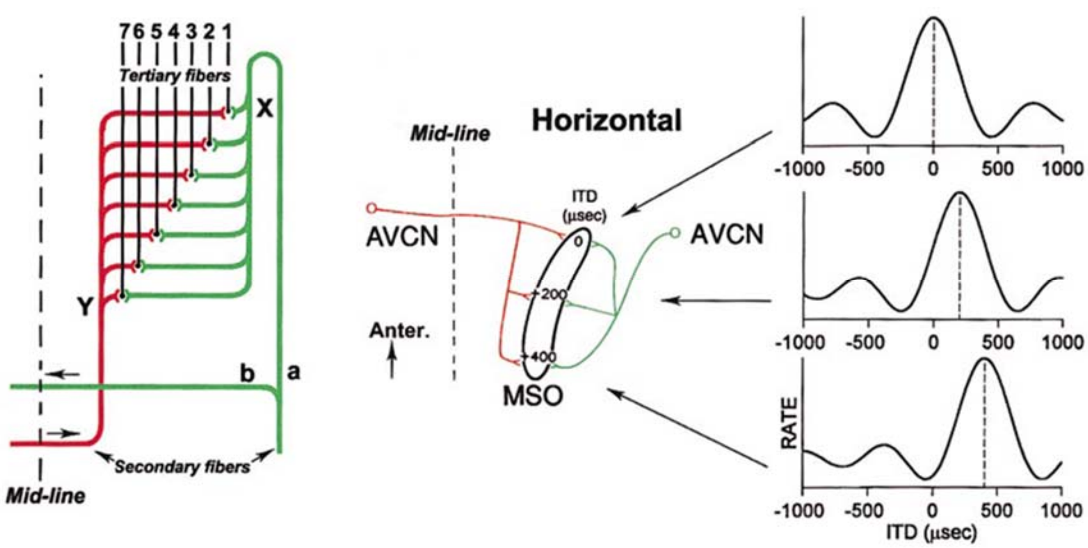

Figure 1-6 Interaural delay lines. Simplified representation of the neural connections responsible for the ITD processing based on the Jeffress model. The left diagram shows the different delay lines from both ears and how they converge into the ITD sensitive neurons. The middle diagram shows three axons with the same length from one ear in green and three axons with different lengths from the other ear in red. On the far right are the corresponding ITD tuning curves showing the corresponding sensitivity of the different ITD groups (Joris et al. 1998).

1.5 Auditory Evoked Potentials

The APs and postsynaptic potentials that are created by the neurons in the auditory system and the brain can be picked using electrodes placed on the scalp. The electrical activity picked up by the electrodes can then be electronically amplified, filtered, digitized, plotted, or recorded. A combination of recordings from multiple electrodes from different portions of the scalp is known as electroencephalography or EEG (Berger 1969). EEG picks up the activity from the entire brain and what can be seen is the dissonant and random activity, with some synchronous activity, originating from different centers in the brain. Similar synchronized activity can be observed when a sound stimulus is presented to a subject. The sound stimulus will evoke synchronous

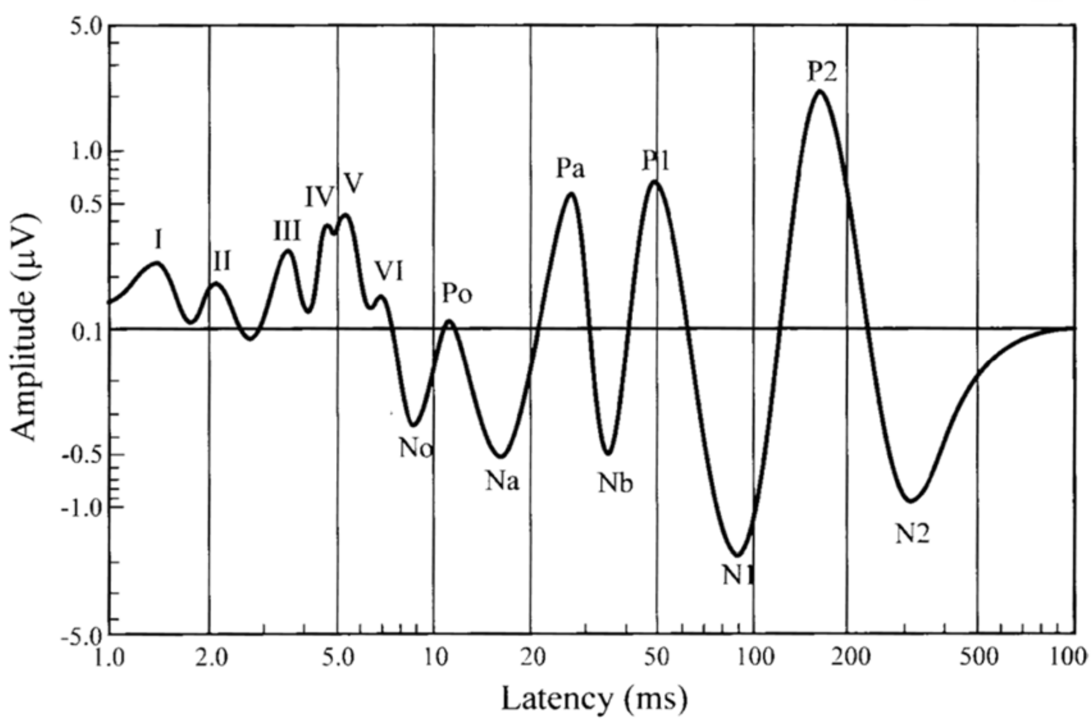

Figure 1-7 Auditory evoked potentials. Auditory Evoked Potentials (AEP) (Picton 2011). AEP on logarithmic amplitude and time scales, showing the three major types of AEP response waveforms. Early or short latency response (0-10ms), middle latency responses(10-50ms), and late latency responses (50ms and later). The logarithmic amplitude and time scales visually amplify and dilate the early and small amplitude responses, while attenuating and compressing the late responses.

activity in the brain which can be picked up using EEG. The responses that are evoked by sound stimuli are called auditory evoked potentials (AEPs) (Picton et al. 1974).

Depending on the acquisition parameters, their origin, and the type of stimulation used, the AEP responses can be divided into three groups. The first group is the early responses that typically originate from the brainstem and are the first ones to appear with latencies up to 10ms. These are also known as auditory brainstem responses (ABRs) based on their neural generators or short latency responses (SLRs) based on to their latencies. After the SLRs are the middle latency responses (MLR) which appear between 10 and 100ms. MLRs are larger in amplitude when compared to SLR and have longer durations. Late latency responses (LLR) follow the MLR and occur after 100 ms and are significantly larger than the SLR (Figure 1-7). The LLR are also referred to late auditory evoked potentials (LAEPs).

LAEPs originate from the activation of multiple areas in the cortex, most prominent of which is the auditory cortex. They are the result of the brain's culmination to changes such as onset or offset of a stimulus (Pantev et al. 1996) or changes in frequency or amplitude (Martin and Boothroyd 2000). LAEPs can also be generated by complex interaural time and phase shifts (Jones et al. 1991) and changes in the location of sounds (Picton 2011). They are characterized by three peaks N_1, P_2, and N_2 with latencies ranging from 50 to 250 ms and amplitudes on the order of microvolts.

LAEPs are affected by the time interval between stimuli, or the stimulus onset asynchrony (SOA). Longer inter stimulus intervals (ISI) will result in LAEPs with larger amplitudes while shorter ISI in smaller amplitudes (Figure 1-8). The amplitudes with respect to the ISI have an exponential behavior which tends to saturate somewhere between 10 and 20 seconds and rapidly decrease for ISI less than 3 seconds (Davis et al. 1966, Hari et al. 1982, Nelson and Lassman 1968).

Increasing the rate of isochronic stimulus delivery, reduces the transient AEP, however at high stimulation rates the evoked potential begin to resemble a sinusoidal waveform with a frequency roughly equal to the stimulus rate. These are auditory steady state responses (ASSRs). They have a frequency component that is equivalent to the rate of the stimuli and remains constant in phase and amplitude for the duration of the stimulation (Picton 2011). They can be recorded using the same EEG montage and synchronous averaging as for transient AEPs.

Rapid presentation of tone-bursts or clicks, due to adaptation of the auditory system, will not evoke detectable LLR or cortical responses. However, the ABR originate strictly from the brainstem as a direct response to the auditory stimulus and are evoked event at high stimulation rates. The ASSR are generally considered to be the result of overlapping ABR.

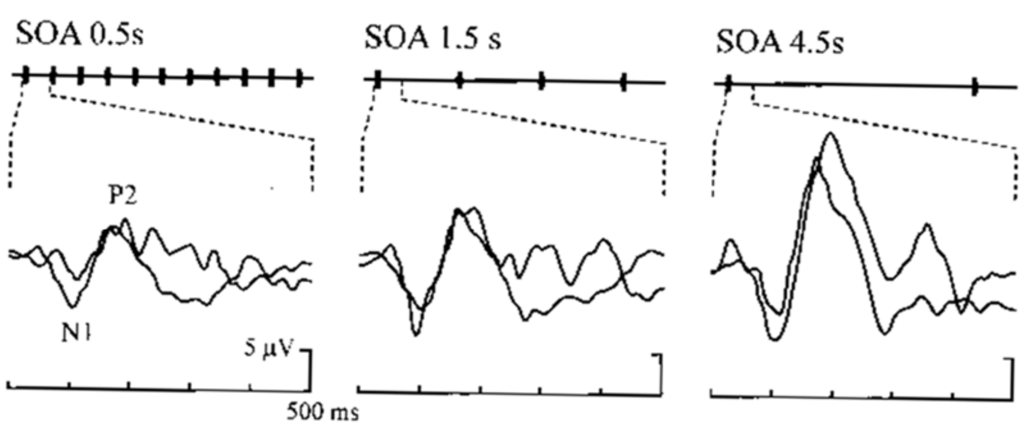

Figure 1-8 Effects of SOA on LAEPs. The figure shows the effects of the SOA on the amplitude of P2-N2.As the SOA decreases the amplitude of the N1-P2 peak decreases. (Picton 2011)

1.6 Frequency Modulation Responses

Sound frequencies are mechanically separated by the cochlea by place coding, where specific regions of the BM inside the cochlea are sensitive to and responsible for a particular frequency band. These frequency regions act as band pass filters and only activate when the correct frequency is introduced.

Frequency modulating (FM) sounds, depending on the modulation magnitude, will intermittently stimulate multiple regions (Békésy and Wever 1960, Novitski et al. 2004). Short transient FMs in a continuous pure-tone stimulus have been shown to evoke

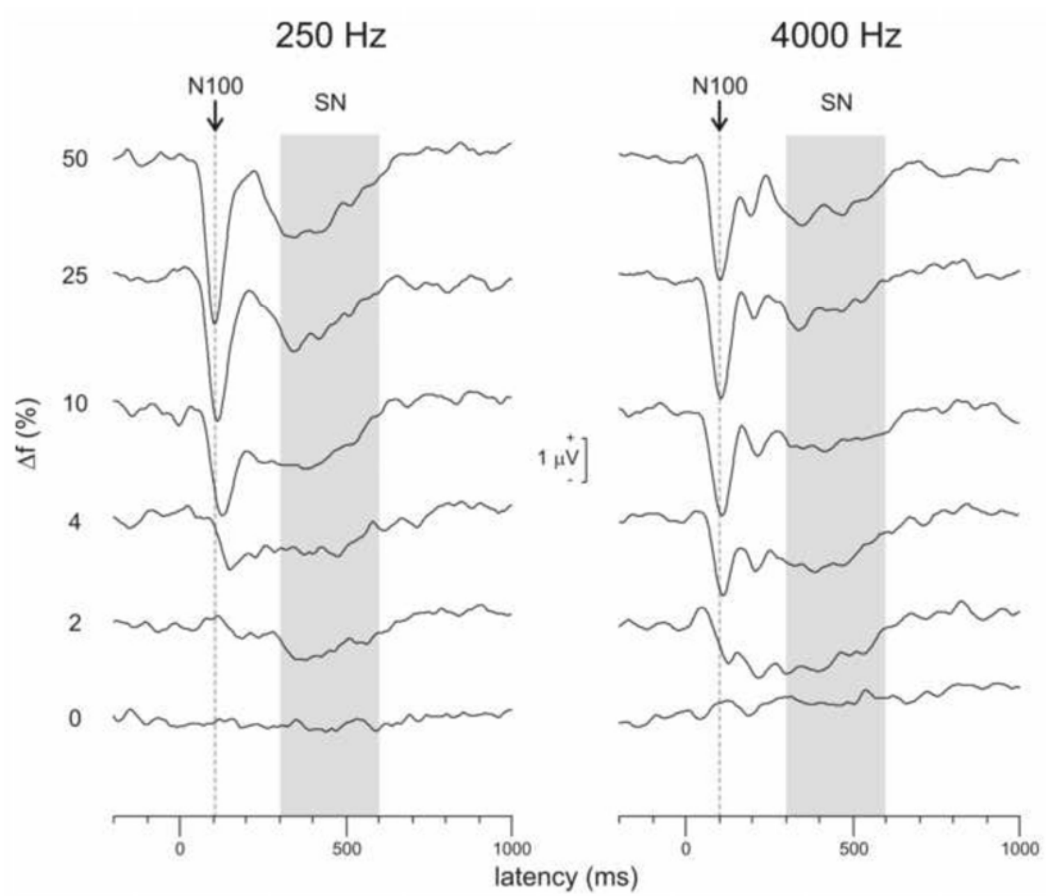

Figure 1-9 AEP evoked by FM sound stimuli. LAEPs evoked by transient FM in continuous pure tone sound of 250 (left) and 4000Hz (right). The magnitude of the FM is a percent ratio of the pure tone frequency. (Dimitrijevic et al. 2008)

LAEPs (Dimitrijevic et al. 2008). The responses to the transient FM were defined by a large N100 negative peak and small P200 peak followed by a slow negativity (Figure 1-9). In their study Dimitrijevic et al. 2008 investigated the effects of frequency changes, %Δf from base frequencies of 250 and 4000Hz. The study showed that the %Δf has a significant effect on the N100 activation amplitudes, for both 250 and 4000HZ, and latency, for 250Hz. Furthermore, a 2%Δf did not elicit any detectable responses for both frequencies.

The frequency sensitivity of a particular neuron can be characterized using tuning curves (Figure 1-10). The tuning curves define the sensitivity of a particular frequency

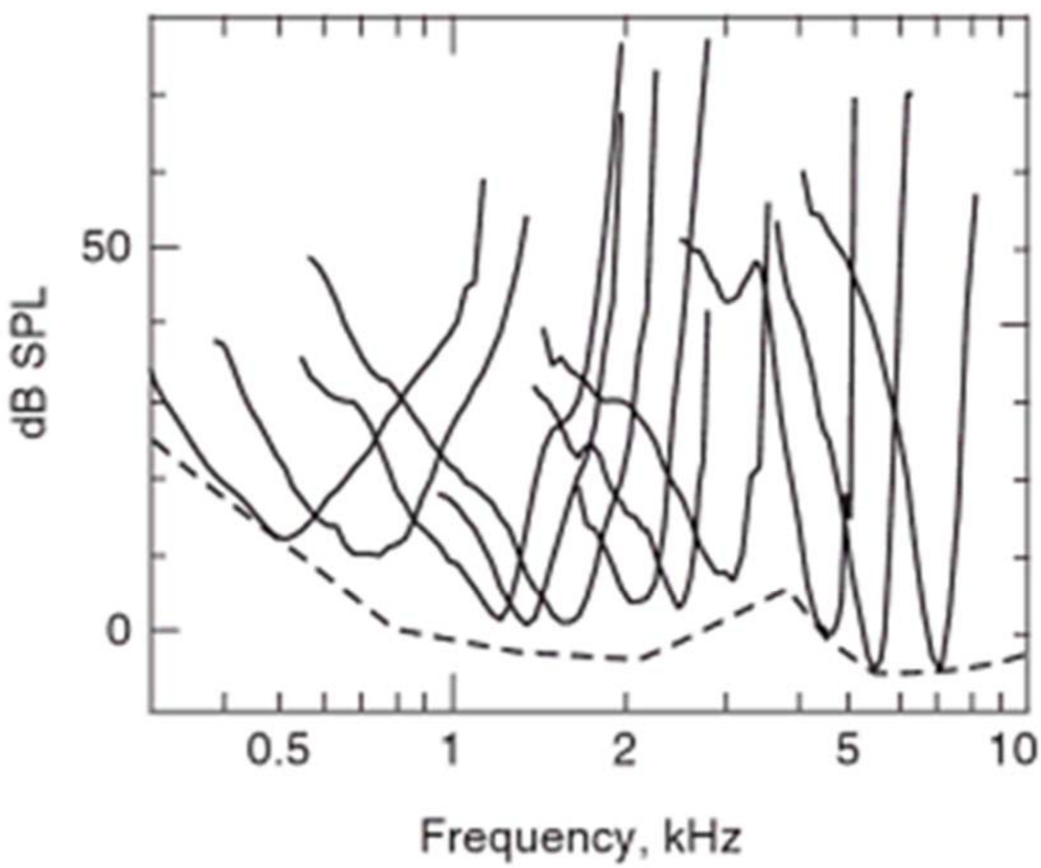

Figure 1-10 Frequency sensitivity bandwidth for specific frequency regions. Tuning curves of the bandwidth of several different frequency specific regions, determined by the activation intensity.(Rees and Palmer 2010)

region to neighboring frequencies in terms of intensity thresholds (Robles and Ruggero 2001, Oxenham 2003). The thresholds define the intensity above the minimum intensity level needed to activate a region on the BM with the center frequency.

FM stimulation, with large enough magnitude, will result in LAEPs to each FM transition, both up and down. The LAEPs are the result of the transient activation and deactivation of two distinct regions on the BM (Dimitrijevic et al. 2008, Pratt et al. 2009b).

1.7 Binaural Beats

The exact location and principles of generation of BBs are not known. However, there is a generally accepted theory that is based on temporal sound localization centers and cues. The phase information of low frequency sounds (<1500Hz) is conveyed as phase-locked APs. The IPD sensitive neurons inside the MSO are innervated by low specific frequency neurons from both ears. These IPD neurons act as coincidence detectors and will only achieve maximal firing if the APs from both ears arrive at the same time (Palmer and Russell 1986, Rose et al. 1968). The lengths of the axons that innervate the IPD sensitive neurons determine the specific phase difference of that particular neuron. However, in the case of 2T BBs the binaural phase is continuously varying over time. The resulting phase-locked APs will trigger activation of different regions in the MSO over time, based on the frequency of the tones and the interaural phase specificity of each region (Wernick and Starr 1968).

Furthermore, binaurally innervated cells sensitive to IPD have been observed along the brain stem, including the IC, in the thalamus and cortex (Spitzer and Semple

1998, McAlpine et al. 1996, McAlpine et al. 1998). The MSO of the SOC is specialized in processing of fine structure IPD that can be activated using BBs. The exact generation of the BBs inside the cortex is not exactly defined.

The BB phenomenon has been under investigation mostly from the psychophysics point of view and just recently in terms of evoked potentials. From the psychophysics perspective, the BBs are perceived as a faint pulsation over a single tone (Licklider et al. 1950). BBs can be generated using two pure-tone (2T) sounds with frequencies no larger than 1500Hz (Licklider et al. 1950, Perrott and Nelson 1969), as shown in the left graph in Figure 1-11. The maximum binaural frequency difference (BFD) at which BBs are detected by ≥50% of subjects is 40Hz. This BFD only applies for stimuli between of 400 to 500Hz (Licklider et al. 1950, Perrott and Nelson 1969), shown with the 500Hz curve in the right plot of Figure 1-11. The two sounds used for BBs may be perceived as two

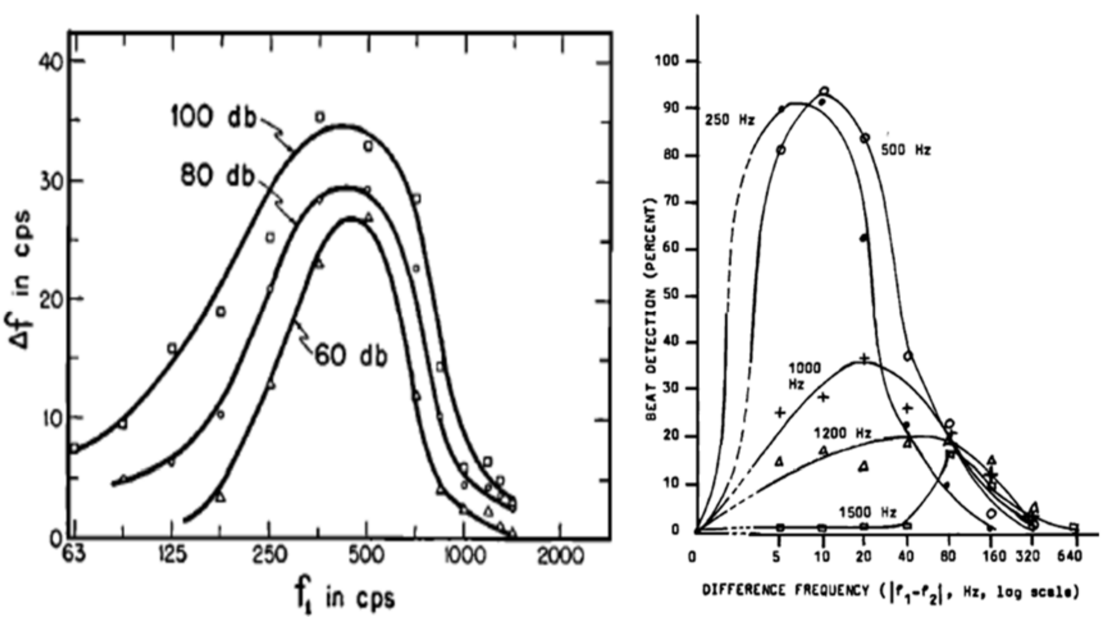

Figure 1-11 Subjective BB detection curves with respect to the base frequency and BFD. The left graph shows the results from (Licklider et al. 1950) in which the maximum BFD that can be subjectively detected at different f_1 frequencies and stimulus intensities. The right graph shows the results from (Perrott and Nelson 1969) showing the rate of detection in % (vertical axis) of BBs for with respect to the BFD (horizontal axis) at several different f_1 frequencies.

distinct tones rather than as BBs if the BFD is larger than 40Hz. According to (Perrott and Nelson 1969) BBs the binaural difference around 10Hz where both stimuli are around 500Hz provide high probability of BB generation and subjective detection. The stimulus intensity may also affect the ability to detect BBs subjectively as seen in the left graph of Figure 1-11.

The upper limit of the two frequencies may be in place as a side effect of the inability of the cochlea to encode the phase information of sounds with frequencies over 1500Hz. The BFD limits may be attributed to the ability of the auditory system to discern between two neighboring frequencies. Furthermore, large BFD will result in slower moving IPD compared to small BFDs.

Studies have shown that the rate of pulsation perceived by the listener is not

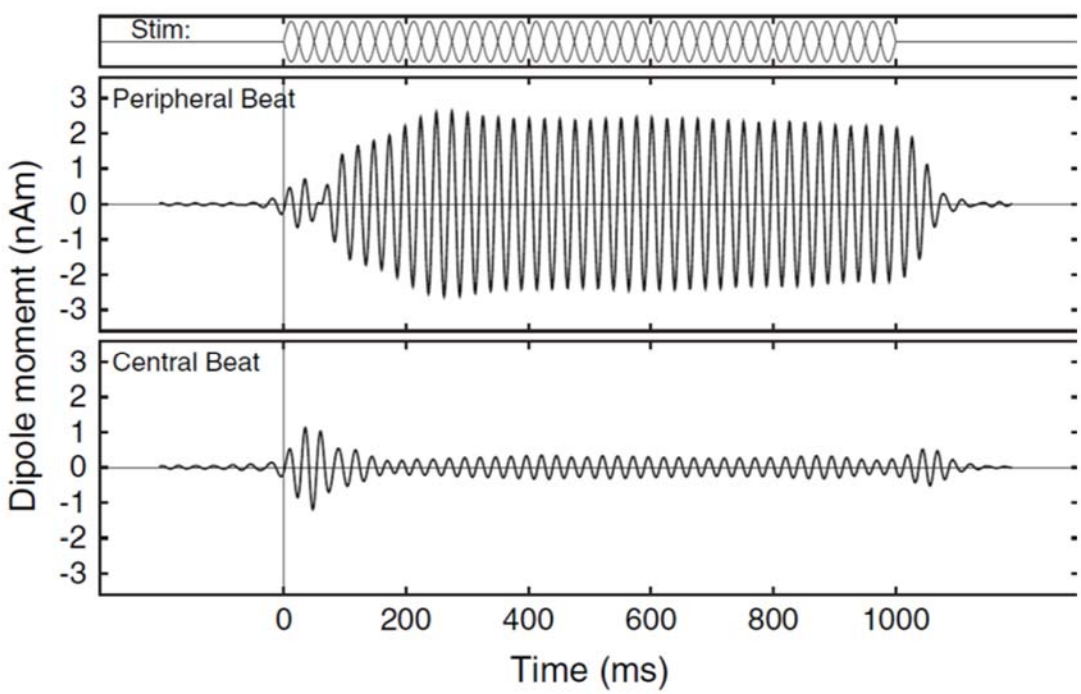

Figure 1-12 MEG grand average of acoustic and binaural beats. Population average of MEG activity in the right cortex from 11 subjects from peripheral, acoustic, beats (top) and central, binaural, beats to 40Hz interaural frequency difference. The stimulus presentation is shown in the top plot to indicate the onset and offset of the stimuli (Draganova et al. 2008).

necessarily equal to the frequency difference of the two sound stimuli. Furthermore, the beating sensation fades after several minutes of continuous stimulation (Fritze 1985). In their study Licklider et al. 1950 were able to determine the subjective thresholds for the maximum frequency difference between the two ears at which beats can be heard. Additionally, they were able to find a working range for the base frequencies at which BB can be perceived (Figure 1-11). It was observed that the base frequencies for BBs have an upper limit of 1500Hz (Licklider et al. 1950, Ross et al. 2007) and the lower varied, depending on intensity, from 63 to 127Hz. The maximal frequency difference threshold varied with both intensity and BFD, however, the maximum was around 35-40Hz with base frequency of around 500Hz (Perrott and Nelson 1969).

Several studies investigated the electrophysiology of BB. In two studies, steady state BB AEP were recorded using stimuli with a base frequency of 400Hz and beating frequency of 40Hz (Schwarz and Taylor 2005, Grose and Mamo 2012). Another study looked at low frequency BB of 3 and 6Hz at 250 and 1000Hz base frequencies tone burst with duration of 2000 ms (Pratt et al. 2009a). This study was able to identify transient responses occurring at the onset and offset of the tone bursts, followed by steady state oscillations corresponding to the beating frequencies. Other studies were able to capture similar BB responses using magneto encephalography (MEG). One of the studies was able to record MEG activity related to 40Hz (Figure 1-12) steady state BB stimulation at 500Hz (Draganova et al. 2008). Another, similar study, was able to acquire using MEG, minimal but distinguishable, responses from low frequency BB, 4 and 6.66Hz, at base frequencies of 240 and 480Hz, by comparing dichotic and diotic stimulation (Karino et al. 2006).

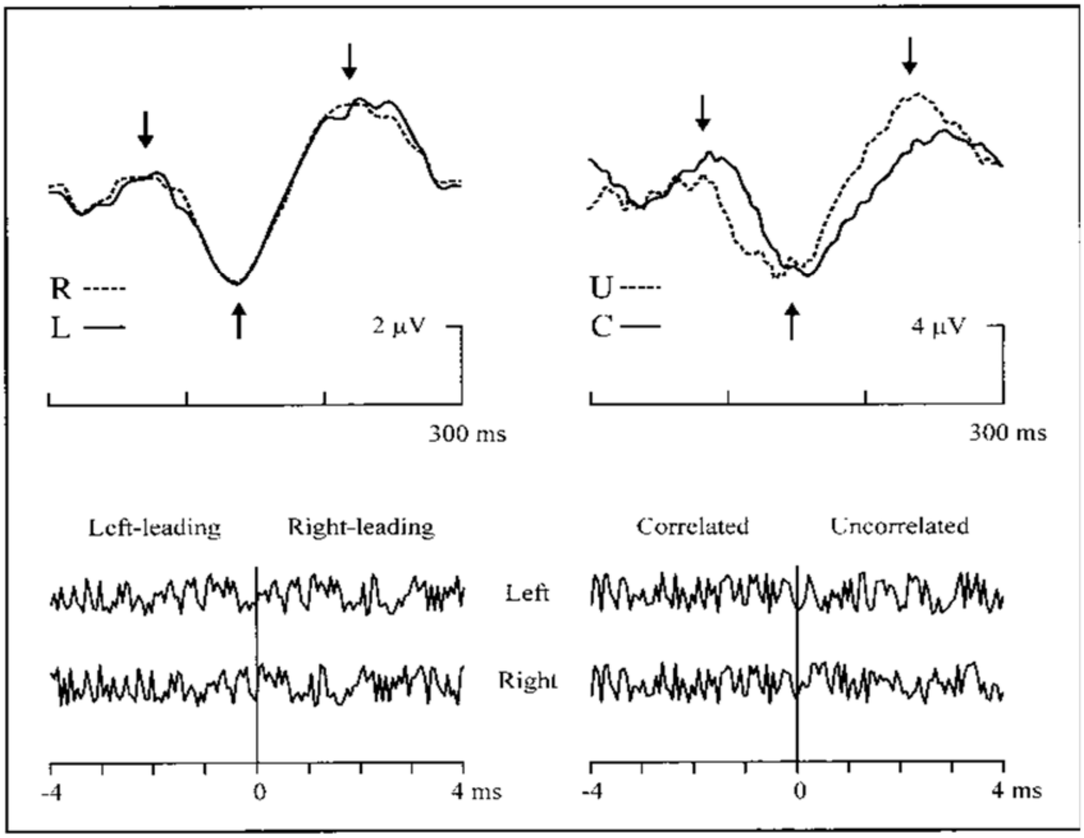

Figure 1-13 White noise stimuli with interaural phase difference and incoherence. White noise stimuli used in the Jones et al. 1991 study (top plots), showing the onset and offset of incoherence between the two ears (left) and the onset and offset of 0.5ms delay in the left and right stimuli (right). AEP responses from the study (bottom plots) show that the phase transitions will evoke late latency responses.

The abovementioned studies used primarily pure-tone stimuli and generated continuous isochronic BBs and only evoked ASSR. Furthermore, the transient AEPs cannot be derived from the isochronic ASSR by means of deconvolution. The set of studies by Jones et al. 1991, Halliday 1978, McEvoy et al. 1990 showed that the interaural phase shift results in a late AEPs characterized by the peaks N1 and P2. In one of the studies (Halliday 1978), the phase shifts were generated by introducing a delay in one of the ears while continuously presenting a train of clicks. Another study (Jones et al. 1991), used binaural white noise in which the phase disparity was generated by introducing a delay in the noise presented to one of the ears (Figure 1-13). This kind of stimulation is advantageous since it allows tighter control over the magnitude and transient behavior of the interaural phase difference. However, it lacks the frequency specificity that applies to the pure-tone stimulation. The study produced late latency responses caused by both the phase delay and interaural coherence and dis-coherence transitions (Figure 1-13).

Chapter 2.
GOALS

2.1 PROPOSED METHOD

The current electrophysiology research on BBs is limited to ASSR, due to the 2T stimulation. However, the transient AEP in most cases convey additional information that is not contained in the ASSR. For this reason most new research on BBs is focused on the topic of transient AEPs. Most of the methods used for evoking transient BB responses (BBR) rely on some kind of AM or disruption of the continuity of the stimuli to switch between beat and no-beat conditions while using pure-tone stimuli. This, however, is not desirable since each disruption in the continuity results in AEPs.

A new method is proposed that generates unitary BBs using FM sounds. The theory is that if two-pure tone stimuli, with equal frequencies, contain a time segment of a BFD they will result in a single or unitary BB. More specifically the duration of the time segment would have to be equal to half of the period of a single cycle of the BFD, since a full cycle will result in two beats (Figure 1-1).

FM can be used to instantaneously change the frequency of the two pure-tone sounds and result in a BFD for a fixed amount of time. However, as mentioned previously, FM can evoke transient AEPs by itself, so the resulting unitary BB AEPs may be evoked by the FM in addition to the BBs.

The main advantage that arises from this stimulus design method is the separation of the rate at which the BBs occur from the rate resulting from the BFD. Since the onset of the unitary BB is directly controlled by the FM, instead of the BFD, the time between consecutive BBs can be arbitrary. This can be used to present the BBs at a slower rate than the one defined by the BFD, which in turn, may provide transient AEPs with larger amplitudes.

2.2 GOALS

The method for evoking transient AEPs to unitary BBs, described in this dissertation, is a relatively new concept that has not been previously investigated in whole. Certain aspects, such as the frequencies of the two sounds, the BFD, and FM evoked AEPs, have been researched and are well documented. However, their interaction, when combined together and used as a method for generating unitary BBs, has not yet been investigated.

The goal of this dissertation was to characterize the effect of some key stimulus design parameters on the AEPs they produce, and the subjective detection and perception of the unitary BBs. Secondary to the characterization was obtaining a set of parameter values that can be further used to generate stimuli that will evoke robust unitary BB AEPs.

Evoked Response Characterization. The preliminary work was performed using values obtained from the literature that have been shown to generate BBs, which can be detected both subjectively and as EPs. However, since this is a new approach to evoked BBs, the initial step must be the characterization of the evoked responses and determine reliable ways of quantify, describing, and analyzing the responses.

Reduction of the FM Responses. After defining the responses evoked by the unitary BBs the next step is the reduction of the FM AEPs that were observed in Özdamar et al. 2011. The goal is to determine the threshold at which FM will not evoke any detectable responses and if the BFD is still large enough to evoke AEPs by itself. The subjective threshold will also be used to determine if unitary BBs can be generated without any subjectively detectable FM. This will determine whether the FM method can be used to generate unitary BBs that can be used to evoke transient AEPs with none or minimal processing of the evoked responses.

Characterization and Optimization. Using FM to generate unitary BBs is a new approach that introduces parameters, which have not been yet characterized or investigated. Some of the parameters, such as the frequencies of the two sounds, are equivalent to the 2T method. However the rate of BB occurrence has not yet been characterized. The final step is the characterization of the effect of some of the key parameters on the evoked responses and the subjective perception of the unitary BBs. Based on the characteristics of the evoked responses, a set of parameter values should result as optimal for evoking robust transient AEPs from unitary BBs reliably and repeatedly.

Due to the scope of work, some of the parameter values were fixed throughout the investigation process and were not parameterized. The method described in this dissertation can be used as a reference for designing stimuli intended for the generation of unitary BBs. Some of the parameter values used in the studies were based on previous research on BBs, while some were restrained and fixed as a rule of thumb. However, the stimulus design offers versatility beyond the scope of this dissertation.

Chapter 3.
METHODS

3.1 Stimulus Design and Generation

3.1.1 Acoustic and Binaural Beats

Acoustic beats are a well-known physical phenomenon that occurs when 2T sounds are presented simultaneously in the same medium and interfere with each other resulting in an AM pure-tone sound. The interference $x(t)$ of the two can be mathematically represented in Equation 3-1 as the sum of two sinusoids with frequencies f_1 and f_2. Using trigonometric identities Equation 3-1 can then be transformed into Equation 3-2 as the product of a sine wave with frequency equal to the average of the two and a cosine wave with a frequency equal to halve of the difference of the two.

$$x(t) = \sin(2\pi f_1 t) + \sin(2\pi f_2 t) \qquad \text{Equation 3-1}$$

$$x(t) = 2\sin\left(2\pi \frac{f_1 + f_2}{2}\, t\right) \cos\left(2\pi \frac{f_1 - f_2}{2}\, t\right) \qquad \text{Equation 3-2}$$

This way, the interference of the two sounds actually resembles the above-mentioned sine wave with a cosine AM envelope depicted in the bottom plot of Figure 1-1. The frequency of the sine component can be referred to as the carrier frequency or f_c while the frequency of the cosine component can be referred to as the beat frequency or f_b .By representing the frequencies f_1 and f_2 as the sum and difference of the f_c and f_b resulting in Equation 3-3.

In Equation 3-3, f_b is equivalent to the rate at which the beats are perceived, due to the fact that one AM cycle consists of a positive and a negative segment and each segment results in a beat, each with inverted polarity relative to the other. The auditory system is not sensitive to the phase difference between two consecutive sounds, hence one full AM cycle results in two beats.

$$f_1 = f_c + \frac{f_b}{2} \; and \; f_2 = f_c - \frac{f_b}{2}$$

$$y(t) = 2\sin(2\pi f_c t)\cos(2\pi \frac{f_b}{2} t)$$

Equation 3-3

On the other hand, if the two sound sources are presented to both ears simultaneously, but acoustically isolated from each other, e.g. using headphones, the result is a binaural beat illusion. Even though the physical interference between the two sounds does not occur, the brain attempts to process the two sounds. The result is an illusion that is perceived as pulsation with a rate equal to the one of the acoustic beats. The BFD produce continuous phase sweeps between the two ears as seen in the middle plot in Figure 1-1 The auditory system attempts to interpret the binaural phase difference as a temporal location cue, but due to the transient phase change, it results in the perception of pulsations or beats.

3.1.2 Frequency Modulating Sounds

Sounds with time varying pitches, or frequencies, are also referred to as frequency modulating (FM) which can be as simple as warbles or chirps and as complex as speech. Pure-tone sounds can be defined as a sinusoid waveform, however, the sine operator only works with angles (***θ)***, so the frequency f of a sine wave can be related to the angular velocity $d\theta/d\tau$ or as the number of 2π radians per second, Equation 3-4 defines the relationship between the angular velocity and the frequency. The instantaneous angle $\theta(t)$ as a function of time can be obtained by integrating the right-hand side of Equation 3-4 over the time t resulting in Equation 3-5 as a constant frequency f or a time dependent frequency function $F(\tau)$. The instantaneous angle can then be used to generate FM waveforms $y(t)$ using the sine operator as in Equation 3-6.

$$\frac{d\theta}{d\tau} = 2\pi f \quad \rightarrow \quad d\theta = 2\pi f d\tau \qquad \text{Equation 3-4}$$

$$\theta(t) = \int_0^t 2\pi f d\tau \quad or \quad \theta(t) = \int_0^t 2\pi F(\tau) d\tau \qquad \text{Equation 3-5}$$

$$y(t) = \sin(\int_0^t 2\pi F(\tau) d\tau) \qquad \text{Equation 3-6}$$

Common practice for FM signals and waveforms is to split the frequency function into three primary components: carrier frequency f_c, modulation frequency f_m, and a time dependent modulation envelope $E(\tau)$. The frequency function can be defined as the sum of the carrier frequency and the product of the modulation frequency and envelope (Equation 3-7). Equation 3-8 then can be used to generate FM waveforms that have a base, or carrier, frequency equal to f_c around which the waveform will modulate according to f_m and $E(\tau)$. The product of the modulation frequency and the envelope dictate the behavior of the waveform with respect to time. The modulation frequency mainly determines the magnitude and direction of modulation, above or below the carrier, while the envelope determines at which point in time the modulation will occur.

$$F(\tau) = f_c + f_m E(\tau)$$ Equation 3-7

$$y(t) = sin\left(2\pi\left[f_c t + f_m \int_0^t E(\tau)d\tau\right]\right)$$ Equation 3-8

Figure 3-1 shows different modulation envelopes and the waveforms they produce. The sinusoid envelope produces FM waveforms with gradual transitions from the carrier to the modulated frequency, while the rectangular envelope produces waveforms with instantaneous transition between frequencies. Both envelopes are constrained between values of 0 and 1. The bottom plots in Figure 3-1 show an example of an envelope starting at 0 and exponentially increasing to 1 resulting in a frequency swept waveform.

Equation 3-8 is defined in the continuous time domain, however, for the purpose of generating waveforms to be delivered using a digital system the equation must be transformed in the discrete time domain (Equation 3-9) where n is a discrete sample in time and f_s is the sampling frequency at which the waveforms will be delivered.

$$y(n) = sin\left(2\pi\left[f_c \frac{n}{f_s} + f_m \frac{1}{f_s} \sum_{i=0}^{n} E(i)\right]\right)$$ Equation 3-9

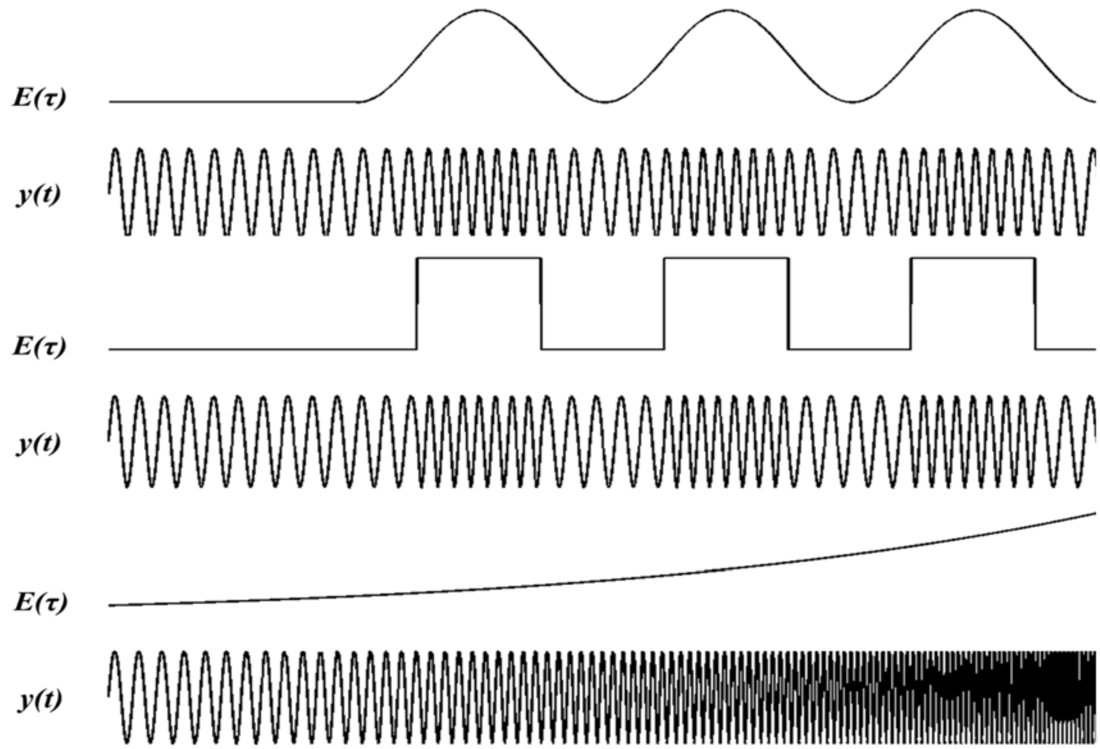

Figure 3-1 Waveforms generated using different shapes of modulation envelopes. Three examples of FM waveforms generated using the method described previously with arbitrary carrier and modulation frequencies. The plots show the waveforms produced (*y(t)*) using a sinusoid, rectangular, and exponential (top to bottom) envelopes *E(τ)*. The sinusoid envelope has a gradual shift from the carrier to the modulated frequency, while the rectangular results an instantaneous shifting between frequencies. The exponential envelope results in a frequency sweep staring at the carrier frequency.

3.1.3 Binaural Beats by Frequency Modulation

Binaural beats are commonly generated using the 2T stimulation method, which has been thoroughly researched from the psychophysical point of view and has well-established foundations. Conversely, the electrophysiology of the 2T method has shown to be more challenging, since the evoked responses are usually steady state oscillations that are also relatively small in amplitude (Pratt et al. 2009a). Furthermore, the 2T method lacks the ability to generate unitary transient BBs without interrupting the presentation of the stimuli and the rate at which beats are presented is proportional to the frequency difference.

A unitary beat can be achieved if the BFD only lasts for the duration of a single beat and no frequency difference for the remainder of the time. Figure 3-2 shows how FM waveforms can be used to generate instantaneous frequency transitions which result in a frequency disparity for the duration of a single beat.

The conventional 2T method, described in Equation 3-2, can be equated to the FM approach, which uses Equation 3-9, in terms of the carrier frequency f_c and the modulation/beat frequency f_m and f_b.

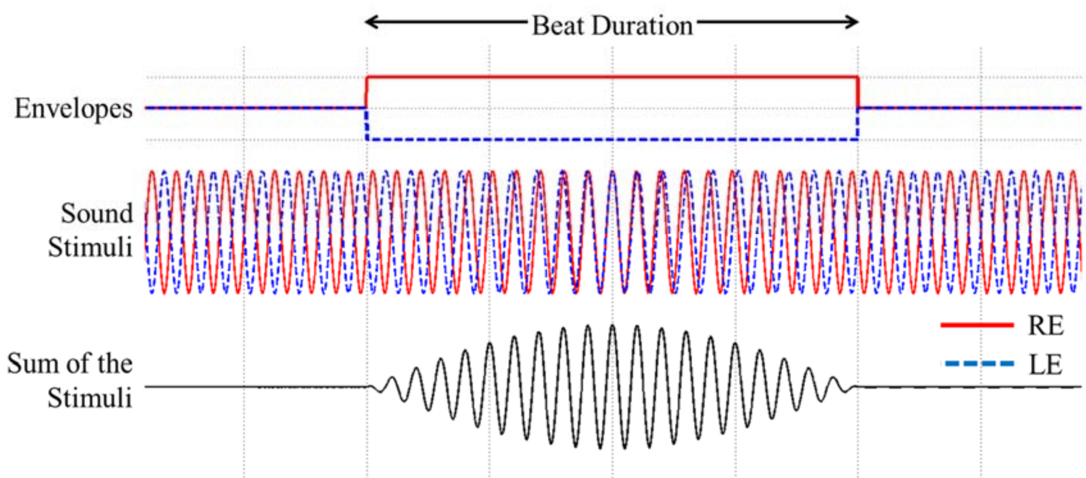

Figure 3-2 Sample configuration used to generate a single unitary binaural beat. The top plot shows the two frequency envelopes used in both ears. Both start at the seame arbitary carrier frequency and modulate with the same magnitude. During the beat portion of the envelope the right stimulus modulates above and the left modulates below the carrier frequency. The middle plot shows the superimposed left and right sound waveforms generated using the frequency envelopes. Before and after the beat portion of the envelope the phase difference between the two stimuli is 180^{o} and at the center point of the beat is 0^{o}. This can be seen in the middle plot where the two stimuli align and in the bottom plot where they add up.

3.1.4 Stimulus Design

For the purpose of generating unitary BBs a rectangular envelope, consisting of ones and zeros, was used since it can generate instantaneous frequency switching. The segments where the envelope has values of "1" will be referred to as **ON** or beat and the segments with "0" will be referred to as **OFF** or no-beat. The time during which the envelope is in the **ON** state will be referred to as the beat duration (BD) or T_{ON}, while the duration of the **OFF** segment will be referred to the as the inter-beat interval (IBI) or T_{OFF}, also shown in Figure 3-4. The frequency of the generated waveforms during the **OFF** segments will be equal to f_c, while during the **ON** segments the frequency will be

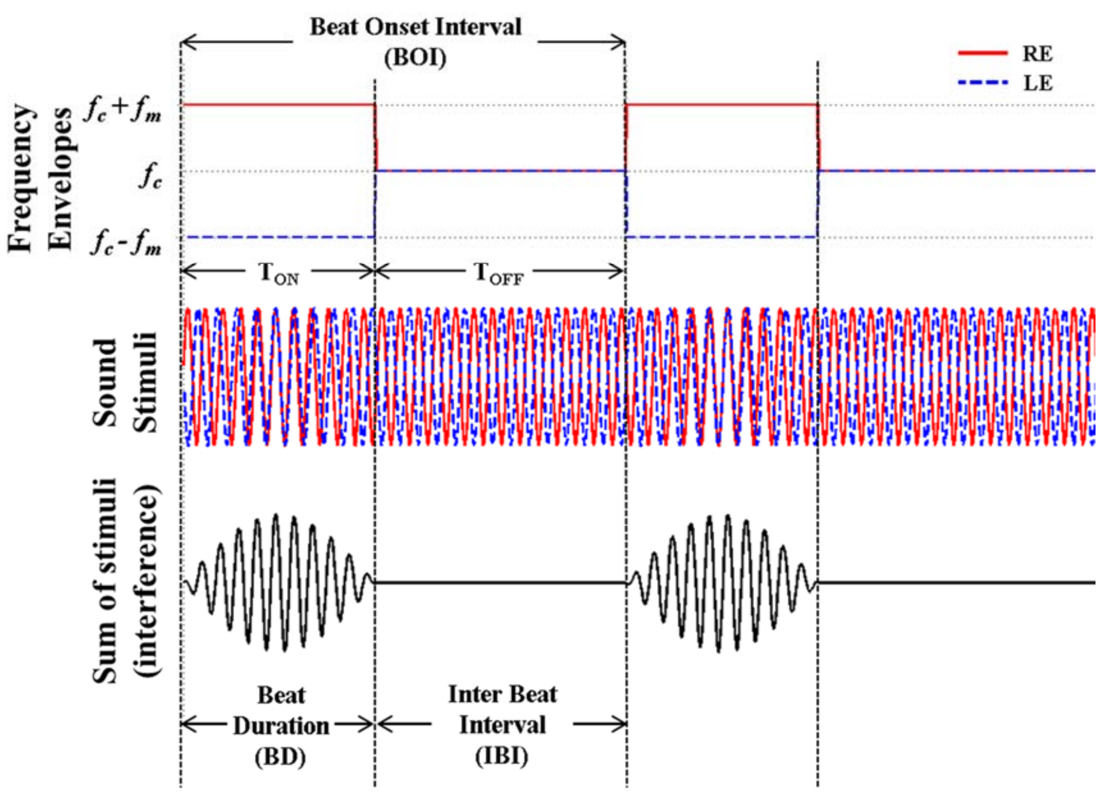

Figure 3-3 Sequence of beats generated using FM waveforms. The top plots show the instantaneous frequency of the waveforms, the middle plot shows the sound waveforms generated for both the left and right ears and superimposed. The bottom plot shows the sum of the left and tight stimuli. The key parameters are labeled accordingly to illustrate their function in the generation of the beats.

equal to $f_c + f_m$. Figure 3-4 shows the behavior of the generated waveforms to their respective frequency envelopes. The left (blue-dashed) stimulus has a negative modulation frequency, so during the **ON** portion the waveform modulates below the carrier frequency, while the right (red) modulates above. This stimulus configuration yields a single beat generated by a frequency difference of $2f_m$ and no frequency difference during the **OFF** segments.

Unitary beats can only be achieved if all parameters and envelopes are configured properly and correctly. Improper configuration may result in multiple beats, phase difference between the two ears, or discontinuities in the waveforms. The carrier frequency is independent of the remainder of the parameters, meaning that changing the carrier frequency will not affect the generation of the beats. From Equation 3-9 can be inferred that the product of the area of the envelope and the modulation frequency control the characteristics of the generated beats.

The number of cycles of a particular segment is equal to the product of the frequency and the time duration of the segment, so the total number of cycles N can be calculated using Equation 3-10, where T_{ON} and T_{OFF} are the time durations of the **ON** and **OFF** segments respectively.

$$N = f_c\, T_{OFF} + (f_c + f_m)T_{ON} \qquad \text{Equation 3-10}$$

Setting f_c equal to zero will result in a waveform with value of zeros during the **OFF** segment and a sinusoid with frequency f_m during the **ON** segment, which can be seen in Figure 3-4, in which the top plot is the product of the envelope and the modulation frequency f_m, the middle plot is the phase of the waveform, and the bottom plot is the actual sinusoid waveform generated by the envelope. The left and right plots show how changes in the duration of the T_{ON} time of the envelope and the modulation frequency will generate the same number of cycles at different frequencies. In the left plots of Figure 3-4 a single cycle is generated using an arbitrary **ON** time duration of $1T_{ON}$ and $1f_m$. Conversely, halving the modulation frequency and doubling the **ON** time will still result in a single cycle, however with frequency equal to $1/_2\, f_m$.

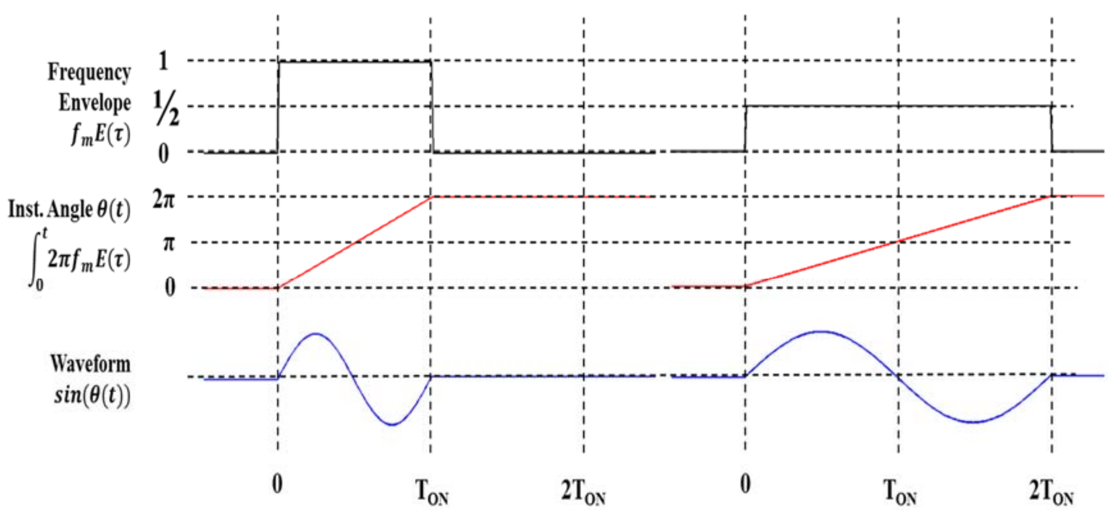

Figure 3-4 The effect of the f_m and T_{ON} on the phase of the generated waveforms. The figure shows the effect of the modulation envelope $E(\tau)$ and the modulation frequency f_m on the generated waveforms. In this case the carrier frequency f_c equals zero. The top plots show the product of the envelope and the modulation frequency, the middle plots show the instantaneous angle $\theta(t)$, and the bottom plots show the generated FM waveform. The left plots show a single sine cycle generated using and arbitrary f_m value of 1 and arbitrary T_{ON} period. The left plots show a configuration with a halved f_m and doubled T_{ON} period, which generated a single sine cycle however with a longer duration.

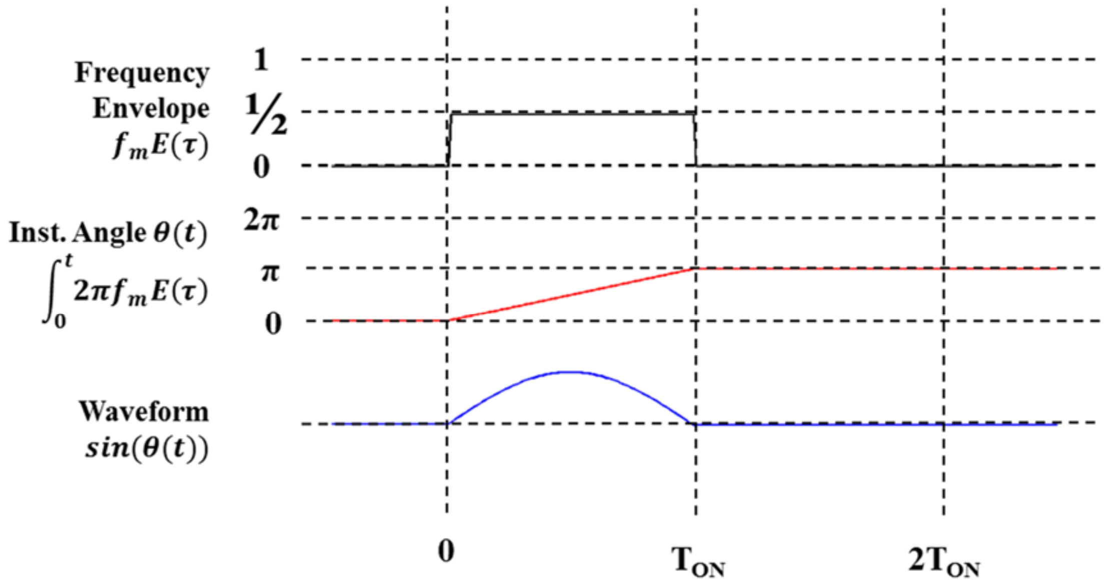

Figure 3-5 Configuration of f_m and T_{ON} that wil produce a unitary BB.The envelope and modulation frequencies configured to generate a single beat by setting the duration of the T_{ON} time to one half of the period of a cycle with a frequency of f_m. In this case the carrier frequency f_c was set to zero to aid the visualization of the waveform during the **ON** segment.

Binaural beats generated using two different frequency tones result in a perceived beating frequency equal to the frequency difference between the two tones, however, the mathematical difference between the two sounds is half of the frequency difference. The perceived beating frequency is the result of positive and negative portions of a single sinusoid cycle and the inability of the human ear to detect the phase and polarity difference between the two. Since the polarity of the beats is not relevant, only a single cycle is needed to generate a unitary beat and this can be achieved by halving both the time duration of the **ON** segment and the f_m in Figure 3-4, resulting in a single cycle waveform in Figure 3-5.

The T_{ON} time must be determined based on the frequency of the waveform $f_c + f_m$ and must be long enough to generate a whole number of cycles for both stimuli. The T_{ON} time required for a complete single beat must be calculated based on Equation

3-11 where the modulation frequencies, $f_{\mathrm{m}L}$ and $f_{\mathrm{m}R}$ are for the left and right respectively. The BFD results in two beats per cycle hence f_b in Equation 3-3 is equal to the beating frequency and same effect can be achieved with the FM method by setting equal, but opposite, modulation frequencies for the left and right stimuli $f_{mL} = -f_{mR}$ which then results in Equation 3-12. Furthermore time T_{ON} necessary to achieve a unitary beat must be equal to the period of f_m.

$$rem\left(T_{ON} \times (f_{mL} + f_c)\right) = rem\left(T_{ON} \times (f_{mR} + f_c)\right) = 0 \qquad \text{Equation 3-11}$$

$$f_{mL} = -f_{mR} \rightarrow f_{mL} = -f_m \; and \; f_{mR} = f_m$$

$$(f_c + f_m) - (f_c - f_m) = 2f_m \qquad \text{Equation 3-12}$$

$$T_{ON} = 1/f_m$$

The time between consecutive beats will be referred to as the beat onset interval (BOI) and is equal to $T_{ON} + T_{OFF}$. Since the T_{OFF} time can be any arbitrary duration and the T_{ON} time is fixed based on the modulation frequency the BOI cannot be smaller than the T_{ON}. Additionally, a BOI of zero will result in consecutive triggering of beats which is equivalent to the 2T method. The flexible T_{OFF} time allows for an arbitrary rate of beat occurrences to be used which is independent from the actual beating frequency.

The resulting stimulus configuration yields two stimuli, one for each ear, where both have the same carrier frequency f_c that determines the base frequency when the two stimuli are in the no-beat condition. Both stimuli have the same modulation frequency f_m that determines the BFD during the beat condition. Additionally, as a convention the f_m of the left stimulus has the same magnitude but is negative relative to the f_m of the right stimulus. This way the BFD is equal to $2f_m$. One modulation envelope $E(\tau)$ can be used to for both stimuli only if the T_{ON} and T_{OFF} times are chosen appropriately. The T_{OFF} time also determines the rate at which the beats will occur and can be varied from one beat to another.

3.1.5 MATLAB Implementation

A Matlab program was developed that automatically determined appropriate parameter values based on the user needs. The program was also capable of generating the stimulus waveforms and saving them to the file format necessary for delivery.

The waveform generation function, documented in Appendix A, is the direct implementation of Equation 3-9. The implementation uses only a rectangular envelope and all beat durations (BD) are equal. Additionally since the integral of the phase at the first sample results in a nonzero value, that value is subtracted from the entire phase array, in order for the waveform to begin with a value of zero.

The Matlab program consisted of a graphical user interface (GUI) that allowed the user to enter the desired parameter values and show a preview of the generated waveforms, their respective envelopes, and the interference of the two (Figure 3-6). Additionally the GUI also provides a plot of two consecutive waveforms which is used by the user to verify the continuity for consecutive stimulus delivery.

The GUI can automatically calculate the modulation frequency f_m or the bead duration T_{ON}, assuming one of them is provided. Additionally the GUI calculates the total duration of the waveform in order to accommodate the necessary ending phase discussed previously.

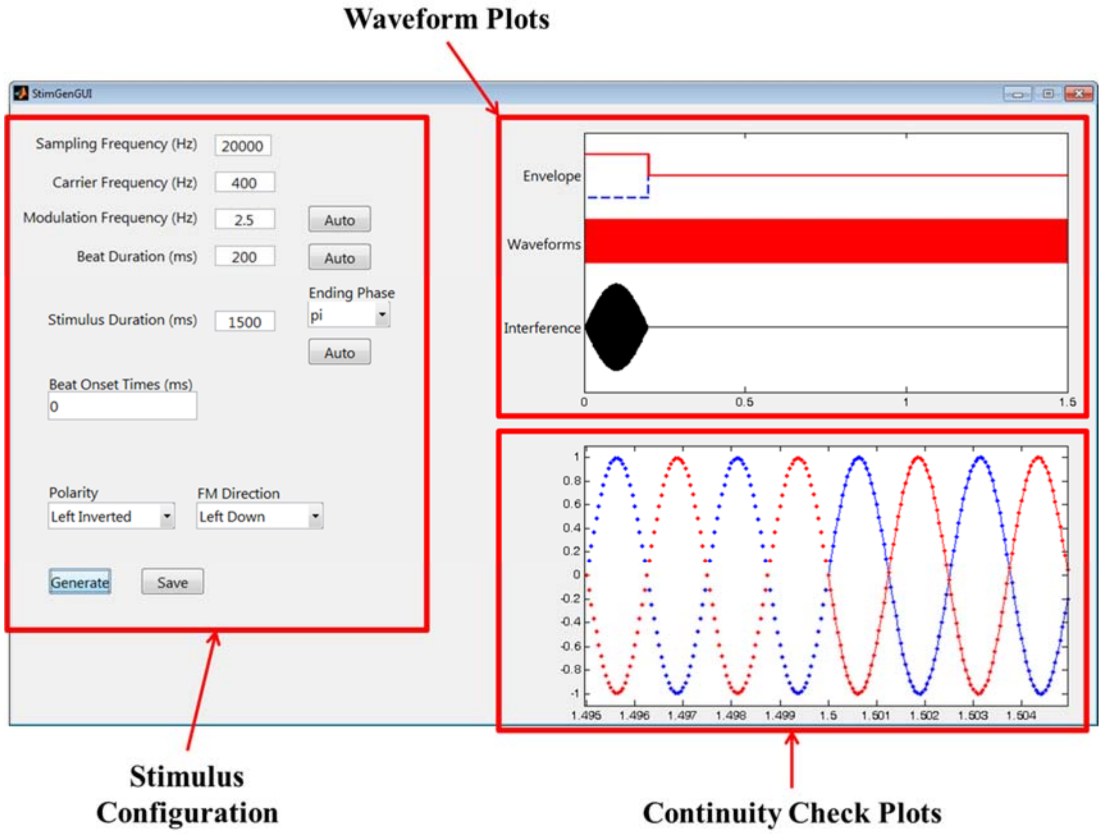

Figure 3-6 Matlab GUI used for the generation of the stimuli. The GUI shows an example of the stimulus generation process with a set of parameters used in the studies. The user can manually input all of the values or can use the automated option to fill certain values within the provided bounds. The generated waveforms are then shown in the **Waveform Plots** together with the envelopes and their interference. The **Continuity Check Plot** shows whether the stimulus can be played continuously without any disruptions.

The GUI was designed for versatility and future expansion of the research, so in addition to the basic beat generation parameters it also allows the user to select different modulation directions, than the one discussed in this dissertation, from the "FM direction" drop-down. Additionally, the used can change the polarity of either the left, right or both stimuli using the "Polarity" drop-down. The example shown in Figure 3-6 only one beat is generated for the duration of the stimulus, however additional BOI times can be added to the "Beat Onset Times (ms)" to generate multiple beats.

3.2 Experimental Setup

3.2.1 Acquisition of AEPs

The binaural beats generated by dichotic FM stimuli are a relatively new concept and have not been thoroughly investigated. Based on existing BB research, the transient responses can be captured using EEG (AEPs) or MEG, but in both cases the responses are predominantly cortical and appear late after the onset of the stimulus. BBs generated using the 2T method typically have steady state responses or oscillations with frequency equal to the difference of the two stimuli. The AEPs, in this case, were acquired using

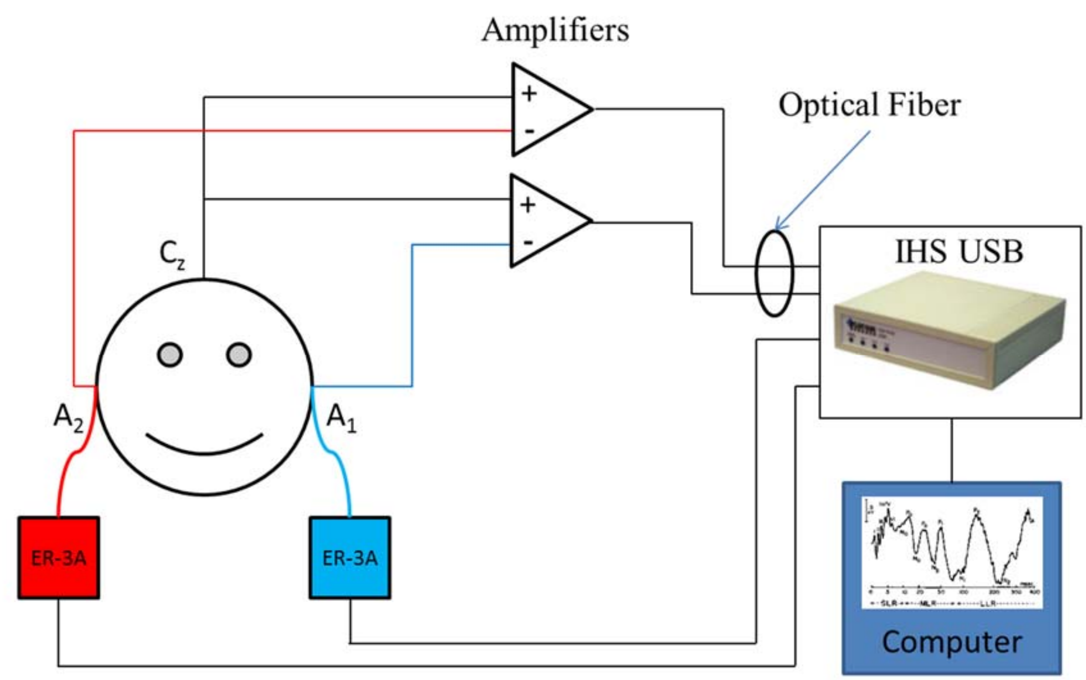

Figure 3-7 Stimulation and AEP acquisition setup for all studies. An IHS USB system was used to deliver the stimuli and acquire the AEPs simultaneously and synchronously. Two EEG channels were used where channel one had the C_Z-A_2 and channel two had the C_Z-A_1 montage. The reference ground was place on the center of the forehead (not shown in the figure). The stimuli were delivered using shielded ER-3A insert earphones and Grass gold-plate scalp electrodes were used to obtain the EEG. The EEG was recorded on a computer and all analysis was performed offline using Matlab.

synchronous stimulation and continuous EEG acquisition. The system used was a two channel Intelligent Hearing Systems (IHS) Universal Smart Box (USB) EEG system. The EEG was sampled at 5000Hz with analog filters from 1-1500Hz (6dB/oct) and two optically isolated instrumentation amplifiers were used to amplify the signals from the electrodes. A standard (10-20) two channel AEP scalp electrode configuration was used where the first channel recorded the electrical potential difference between the apex of the head, and the right mastoid (C_z-A_2), channel two was recorded from the apex and the left mastoid (C_z-A_1), and the common ground was referenced to the forehead.

The sound stimuli were delivered to the subject from the IHS system using Etymotic Research (ER-3A) insert earphones with silicone tubes, which allow the transducer to be placed further away from the electrodes reducing the electromagnetic (EM) interference caused by the electromagnets and movement of the magnets inside the transducers. Additionally, the transducers were enclosed in a mu-metal enclosure which further reduces the EM interference.

The sound stimuli were generated using Matlab and were converted and calibrated for delivery by the IHS system. The sound was generated with a sampling frequency of 20kHz and amplitude resolution of 16bits. All of the sound levels were kept at levels below the maximum allowed threshold for long duration sound exposure.

The AEP were obtained by continuous EEG acquisition and averaging of fixed length time windows called epochs or sweeps. The length of the sweeps was determined by the length of the stimuli or the BOI. Even and odd numbered sweeps were averaged into two separate buffers. Sweeps with amplitudes above 45 µV or below -45 µV were rejected and not included in the buffers when averaging. This averaging method allows the signal to noise ratio (SNR) to be calculated by averaging the two buffers to obtain the signal and half the difference of the two to obtain the noise; the SNR was used to quantify the quality of the recordings or responses. In addition to the SNR, visually overlaying the two buffers on top of the averaged responses gives a visual representation of the quality of the responses, which was used as an aid in determining the amplitudes and latencies of the peaks. Unless specified otherwise, all of the recordings consisted of 512 accepted sweeps, where each condition was segmented into four recordings of 128 sweeps and the segments were recorded in a latin square configuration in order to distribute any effects of throughout the recording session.

All of the EEG recordings were performed in a double-walled sound attenuated booth, shielded from electromagnetic interference. The subjects were comfortably lying down on a bed to reduce any noise that could be introduced from muscle activity. The subjects were shown a muted and captioned movie of their choice to keep them alert, awake, and distracted from the sound stimuli. Before any recordings were performed all subjects signed an informed consent form according to the University of Miami Institutional Review Board (IRB). All subjects did not have any apparent hearing disorders and all subjects had pure-tone audiometry performed to verify that their hearing thresholds were below 25 dBHL.

3.2.2 Stimulation and Stimulus Configurations

The primary purpose of this dissertation was to characterize the responses from unitary BBs generate using FM stimuli and optimize some of the stimulus parameters in order to achieve a set of values, which can then be used to generate consistent and repeatable responses. In order to simplify the optimization process certain restrictions to the stimulus parameters had to be applied. The envelope was restricted to a rectangular (**ON**/**OFF**) shape where the beat only occurs during the **ON** segments. The rectangular envelope was configured according to Equation 3-12. The modulation magnitudes were equal for both ears; however the modulation direction for the right stimulus was above the carrier and below the carrier for the left ear. The modulation frequency must be kept

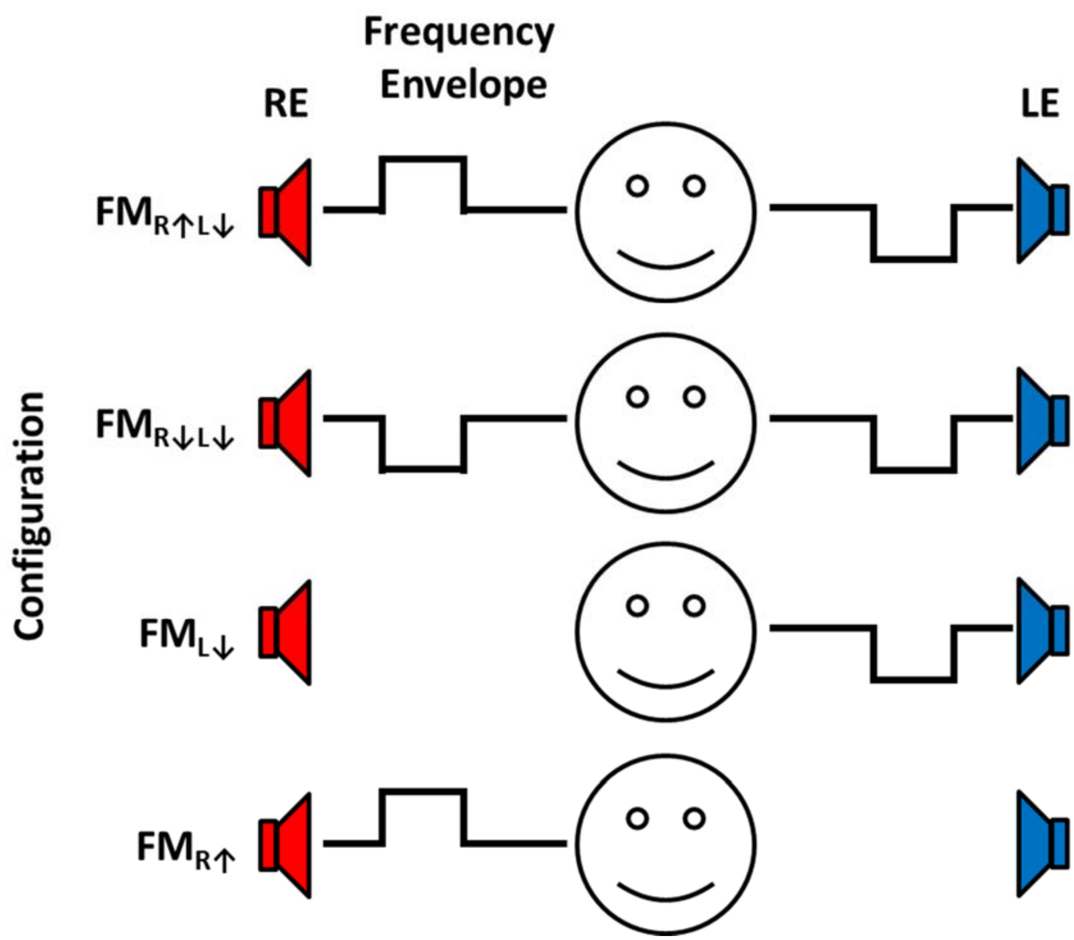

Figure 3-8 Stimulation configurations.
The figure shows four different stimulation configurations. The top two are binaural and the bottom two are monaural. The top configuration is binaural-dichotic and is intended for the generation of unitary beats. The second from the top is binaural-diotic and is intended for generating binaural FM stimuli, without beats, to capture the responses evoked only by the FM. The nomenclature describes the type of stimulation, in this case FM, the ears stimulated R or L, and the direction of modulation relative to the carrier frequency for the corresponding ear.

at a minimum in order to reduce any AEPs from the FM. The variable parameters were the carrier frequency f_c, the modulation frequency f_m, BD, BOI or the beat rate**,** and the stimulus intensity.

The stimuli were generated offline using Matlab and then preloaded into the stimulation system where one stimulus presentation was one sweep. The polarity of the stimuli was alternated between sweeps in order to reduce any frequency following responses which may have been generated by the pure tone stimuli. To achieve uninterrupted presentation between sweeps, the stimuli ended at a phase of $\left(1-\frac{1}{f_s}\right)180°$. The polarity of the left stimulus was inverted so that the sum of the two stimuli during the **OFF** segments result in destructive interference and cancel each other.

Several stimulation configurations (Figure 3-8) were used and classified based on the type of stimulation and the stimuli that were delivered. The nomenclature of the stimulation configuration was determined by the ears stimulated and the direction of modulation with respect to the carrier frequency f_c. So, $FM_{R\uparrow L\downarrow}$ indicates an FM and binaural-dichotic stimulation in which the stimulus to the right ear modulates above and the left below f_c. Following the same pattern $FM_{R\downarrow L\downarrow}$ is diotic stimulation where both stimuli modulate below f_c and $FM_{R\uparrow}$ or $FM_{L\downarrow}$ are monaural stimulations. Based on the stimulation method and stimulus parameters the responses can be classified as binaural beat responses (BBR) which result from the frequency difference between the two ears and frequency modulating responses (FMR) which result from the changes in frequency of the sound f_m. However, if f_m is large enough and f_c is within the range for generating BBs both BBR and FMR will be generated and result into a single compound response (CR) (Özdamar et al. 2011). Since the responses are LLRs, the interaction of the BBR and FMR is non-linear, so they cannot be subtracted from the compound response to get the individual components (Picton 2011).

3.2.3 Experimental Setup for Stimulus Characterization

The stimuli parameters were optimized by varying one parameter while keeping the remainder constant. Several studies and protocols were designed to evaluate the individual parameters, like the f_c, the f_m and BD, beating rate and the BOI, and the stimulus intensity. The studies were named after the parameter tested, ex. frequency for the carrier frequency or duration for the beat duration.

The parameter of greatest interest was the f_m because if large enough it will elicit BCR and since the primary focus were the BBR an attempt to find an optimal f_m was made by reducing it to a level where the FMR will diminish while the BBR remain above the noise floor. The first study was designed to characterize the FMR and BCR across a set of four f_m frequencies. The different f_m were recorded both with dichotic ($FM_{R\uparrow L\downarrow}$) and diotic ($FM_{R\downarrow L\downarrow}$) configurations where the $FM_{R\uparrow L\downarrow}$ was used to record the BCR while the $FM_{R\downarrow L\downarrow}$ was used to record the FMR. The values for f_m and BD were calculated according to Equation 3-12 and the set of f_m with their corresponding BD used was: 20Hz/25ms, 10Hz/50ms, 5Hz/100ms, and 2.5Hz/200ms. The carrier frequency f_C was set to 400Hz, the IBI was set to 1second and the intensity was 75 dBSPL (Özdamar et al. 2011). The conditions of this study were recorded as single blocks of 512 sweeps.

The second parameter investigated was the rate of beat occurrences and the BOI, since the responses are ERP and predominantly cortical they should be sensitive to the rate of beat occurrences, more specifically they tend to increase in magnitude with slower rates and vice versa at higher rates (Picton 2011). For this study a compromise had to be made between the BOI and the total recording time, because increasing the BOI proportionately increases the sweep duration. The set of BOI times used for the study were 0.5s, 1.0s, 1.5s, and 3.0s. The lower boundary, 0.5s, was set to provide enough time for the responses to diminish without overlap from consecutive beats and the upper limit was set to 3.0s so that the total recording session time did not exceed 2 hours. The f_c in this study was fixed at 400Hz with f_m/BD equal to 2.5 Hz/200ms (Mihajloski et al. 2014), and intensity of 75 dBSPL. The purpose of this study was to characterize the effects of the BOI on the BBR and to find an optimal BOI which can be used to generate robust and repeatable BBRs.

The effects of the carrier frequency f_c on the responses was investigated in a previous study (Özdamar et al. 2011) in which it was concluded that the FM BB method can be used to generate BBR. The study used a short BD (25ms) and relatively high f_m (20 Hz) to investigate the BBR. The study used a dichotic configuration $FM_{R\uparrow L\downarrow}$ configuration and two monaural configurations, $FM_{R\uparrow}$ and $FM_{L\downarrow}$. The results of the study showed that the f_m used was large enough to elicit FMR and that the responses from the $FM_{R\uparrow L\downarrow}$ were CR. Furthermore, the study showed that the FMR were distinguishable from the BCR indicating that there must be another generator contributing to the BCR in addition to the FM. The third study looked into f_c, however, in this case the f_m was significantly smaller (2.5 Hz) (Mihajloski et al. 2014). The study used the same set of carrier frequencies as in the above mentioned frequency study (250, 400, 500, 750, 1000, 1500, and 2000 Hz). Additionally, the value of BOI used in this study was determined in the previously mentioned BOI study and was equal to 1.5s. The intensity was set to 70dBHL (ISO 389.2) which was equal to 75 dBSPL at 400 Hz and 70 dBHL at 1 kHz. The stimulation configuration was $FM_{R\uparrow L\downarrow}$ for all frequencies. In addition to the dichotic stimulation one diotic ($FM_{R\downarrow L\downarrow}$) recording segment of 128 sweeps was performed to verify that the f_m is small enough at 250 Hz not to evoke any FMR. The diotic stimulation was not necessary for frequencies above 400 Hz since the relative ratio of f_m to f_c is smaller or equal to 0.625 % at 400 Hz, however, at 250 Hz the ratio 1.0% is greater and might elicit FMR.

The intensity of the stimulus was investigated in order to determine how sensitive the responses are to changes in intensity and to determine if there might affect the results from the carrier frequency study and whether dBSPL or dBHL standard values at different frequencies might be affecting the responses. In this study the intensity was varied from 25 to 75 dBSPL (20 to 70 dBHL) at 400 Hz in increments of 10dB. The remaining parameters were fixed with f_c equal to 400 Hz, f_m was equal to 2.5 Hz, and the BOI was equal to 1.5s. This study was also used to determine the electrophysiological threshold for BBR. In addition to the AEP recordings the subjects were also asked to subjectively determine whether they hear the BB or the stimuli at different intensities.

The last study performed was a combination of the f_m and the f_c studies, but instead of AEPs the subjects were tested for their psychophysical thresholds of beat and frequency modulation perception. This purpose of this study was to characterize the subjective thresholds for BB and FM over a range of f_m and f_c, Two stimulation configurations were used; $FM_{R\uparrow L\downarrow}$ to determine the BB threshold and $FM_{R\downarrow L\downarrow}$ to determine the FM threshold. In both stimulation configurations the subjects were presented with continuous stimuli, similar to the ones used in the previous studies, and were asked to indicate the presence or absence of deviations of any kind in the presented stimuli. Each presentation was a single combination of f_c and f_m. The set of values used for f_c was the same as the one used in the third study (carrier frequency) and the f_m ranged from 0.5 to 12 Hz in half octave increments. The main goal of this study was to determine the psychophysical range for the carrier frequency where FM BBs can be generated and perceived, and to determine the threshold at which the perceived pulsations are from the BFD, or from the FM.

Chapter 4.
RESULTS

4.1 Response Characterization

4.1.1 Response Waveform Morphology

The AEP responses observed in most cases can be described as a quad-phasic waveform consisting of two positive peaks, labeled as P1 and P2, and two negative peaks N1 and N2 (Figure 4-1). In most cases, the latencies relative to the onset of a beat were around 75 ms for P1, 120 ms for N1, 195 ms for P2, and 330 ms for N2. The amplitudes

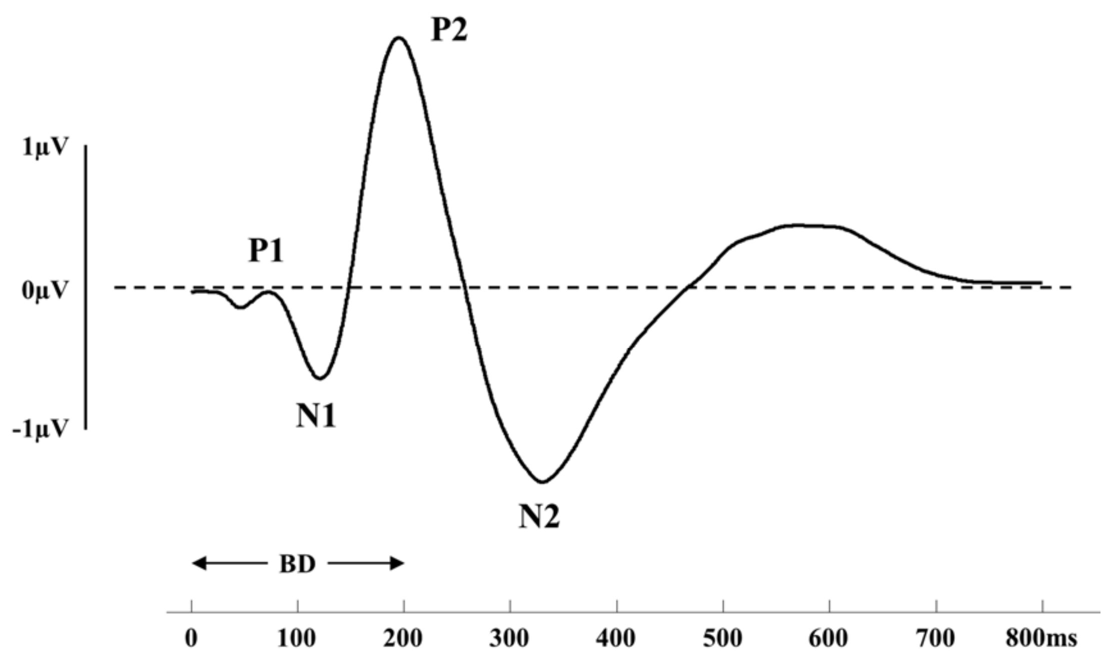

Figure 4-1 Population average showing the typical response waveofrm observed in the studies. Both channels of 24 subjects were combined to generate the population average using stimuli with f_c of 250-400Hz, f_m of 2.5 to 25Hz / BD 200 to 20ms, BOI of 1.5s, and intensity of 75 dBSPL. The process by which this figure was obtained is described in detail in Appendix B.

of the peaks ranged in microvolts and significantly varied in magnitude between subjects and conditions. The responses diminish after 400 ms even though a slow positive wave can be seen in Figure 4-1 at 600ms. This slow wave typically can be seen when large numbers of subjects and conditions are averaged together. The early responses, prior to P1, in most cases were difficult to detect due to the small amplitudes, small number of averaged sweeps, and large noise levels.

4.1.2 Response Variability

The responses in all studies were recorded using two channels, one from the right mastoid (C_z-A_2) and the other from the left (C_z-A_1), however, the two channels did not show any correlation to the stimulus parameters. The population averages (N=7) of the two channels depicted in Figure 4-2 show only small amplitude variations while the latencies remained consistent between the two. The peak P1 had the same absolute amplitude magnitude in both channels, while the peaks N1 and N2 had larger absolute magnitudes in the right channel relative to the left. The overall morphology of the AEP was consistent between the two channels, with the exception with the sharp N2 peak in the right channel.

The general morphology, shown in Figure 4-1, of the response waveforms was consistently present throughout all subjects and most conditions. The peak P1 was not detectable in most cases due to large slow early potentials and amplitude shifts at the beginning of the response waveforms.

Figure 4-3 shows a set of subjects, all recorded with the same condition, and their response variances. The peaks N1 and P2 are the most consistent throughout all subjects, however, with minor shifts in latency and variations in amplitude. Subjects 1-3 showed the most resemblance to the population average (top plot in Figure 4-3) in terms of peak latency, amplitude, and general morphology. On the other hand, subject 4 had a more distorted morphology with a broadened peak P2 and small amplitude N1 and N2. The peak N1 was also delayed about 30-40 ms relative to the population average. Subject 5 elicited responses with latencies and amplitudes closely matching the population average, in contrast to the average, the peak P2 had a two-step descent into N2. Subject 6 had an

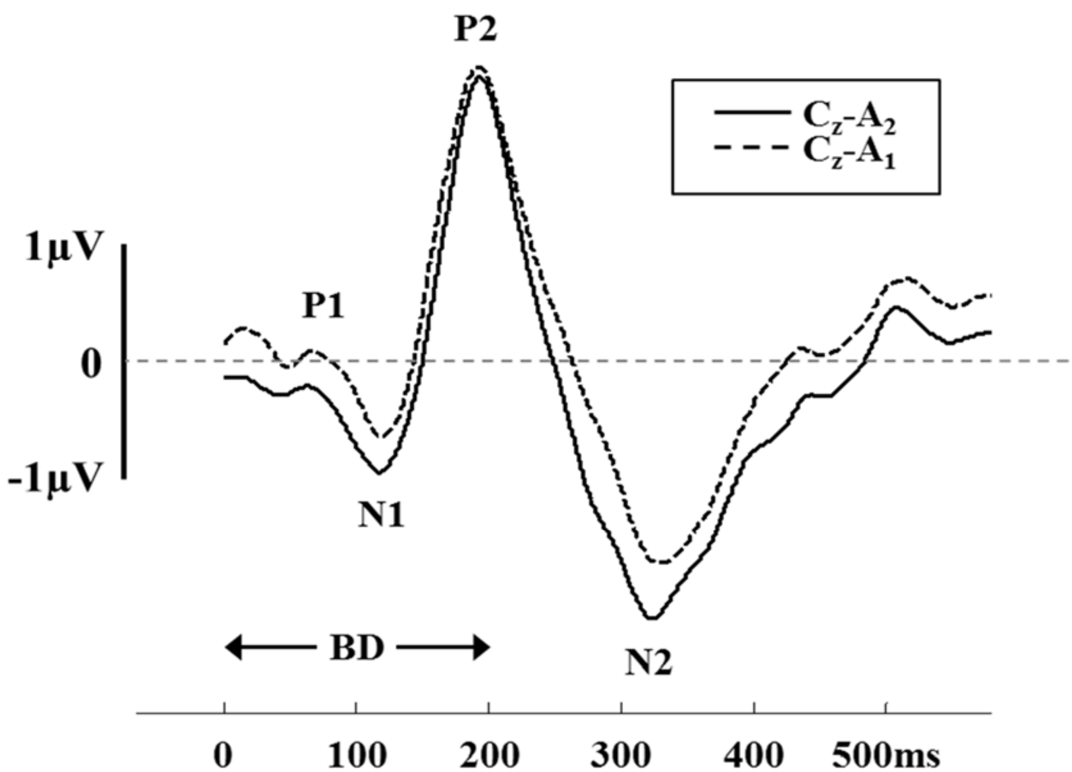

Figure 4-2 AEP from C_z-A_2 and C_z-A_1. The figure shows population averages (N=7) of the two recorded channels. The right hemisphere (C_z-A_2) is shown in a solid black line and the left hemisphere (C_z-A_1) is shown in a dashed black line. The zero reference is shown as the horizontal dashed line. The beat duration (BD) was placed underneath the responses as frame of reference. The responses were obtained using a stimulus with f_c of 400Hz, f_m of 2.5Hz / BD of 200ms, BOI of 1.5s, and intensity of 75 dBSPL.

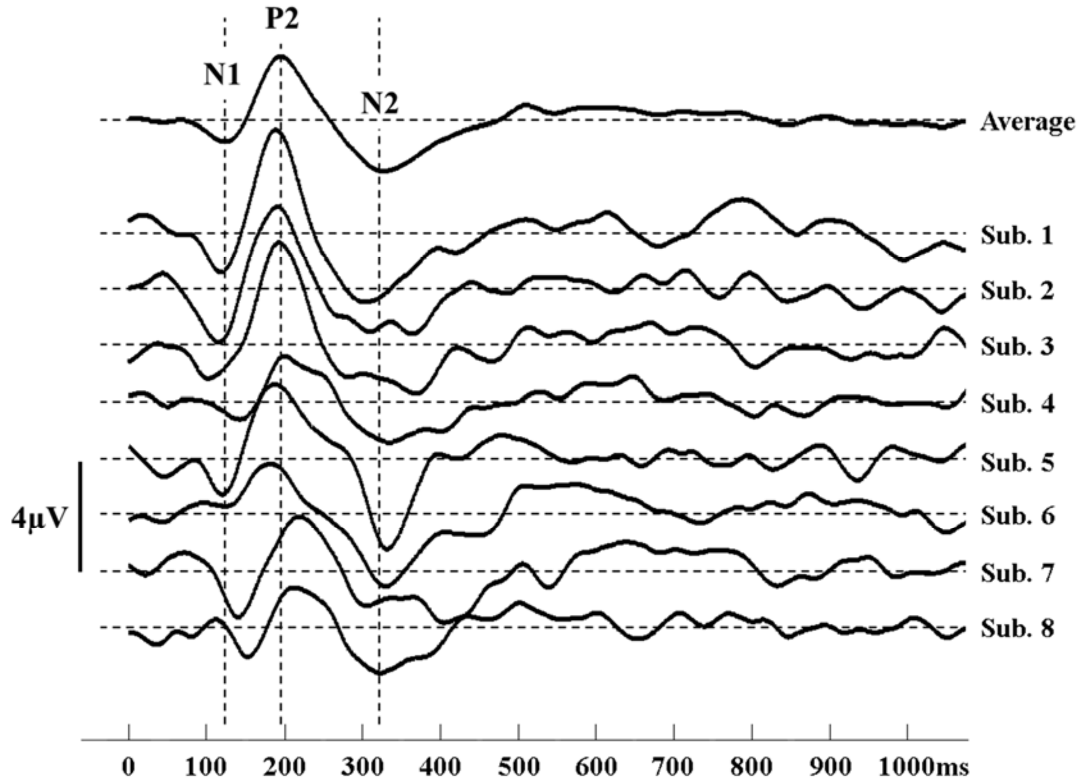

Figure 4-3 Response variability across subjects. The indivdual subject responses were obtained using f_c of 400Hz, f_m/BD of 2.5Hz/ 200ms, BOI of 1.5s, and intensity of 75 dBSPL. The responses were all filtered with a second order low-pass butterworth filter. Subjects 1, 2, 5, 7 and 8 are males with ages 27, 29, 20, 27, and 21 respectively. Subjects 3, 4, and 6 are females with ages 27, 20, and 20 respectively. The vertical lines are the latencies of the three main peaks with respect to the population average (top).

N1 peak with a positive value contrary to the population average, while the peaks P2 and N2 complimented the average. Subjects 7 and 8 showed a general shift in latency by approximately 50 ms for all peaks. Overall, the responses observed in Figure 4-3 showed consistency mostly in the latency of occurrence of the three main peaks (N1, P2, and N2).

4.1.3 Response Analysis and Quantization

The individual responses from all subjects were grouped based on the condition of interest and averaged together to make the population or grand averages. The grand averages together with the individual subject plots were used as a qualitative representation of the responses to determine if any visually apparent trends were present between the test conditions and the responses.

The responses, in addition to the qualitative representation, were quantified using manual peak measurements of detectable peaks. The amplitudes and latencies of P1, N1, P2, and N2 were measure and tabulated for each subject and condition. However, the inter-peak difference P1-N1, N1-P2 and P2-N2, both amplitude and latency, were used in the quantitative analysis of the results. The descriptive statistics of the inter-peak measurements were calculated and tabulated in Appendix C.

The descriptive statistics were then visualized using box and whicker plots along with the population means for each condition. In addition to the descriptive statistics, analysis of variance (ANOVA) was performed to determine the significance of the effect that both the stimulus parameter of interest and the subjects had on the evoked responses. The two-way ANOVA was performed only on groups which had similar sizes. The detailed results of the ANOVA were tabulated in Appendix D, while a brief summary showing the F-values, with the corresponding degrees of freedom (in brackets), and the p-values were tabulated for each study individually.

4.2 The Effects of the Modulation Frequency

The responses obtained using the new BB stimulation method produce BCR consisting of FMR and BBR. The goal of this study was to characterize the BCRs and determine whether the FMRs can be reduced while still preserving the BBR. For this study, the $FM_{R\uparrow L\downarrow}$ and $FM_{R\downarrow L\downarrow}$ stimulation configurations were recorded from 8 subjects

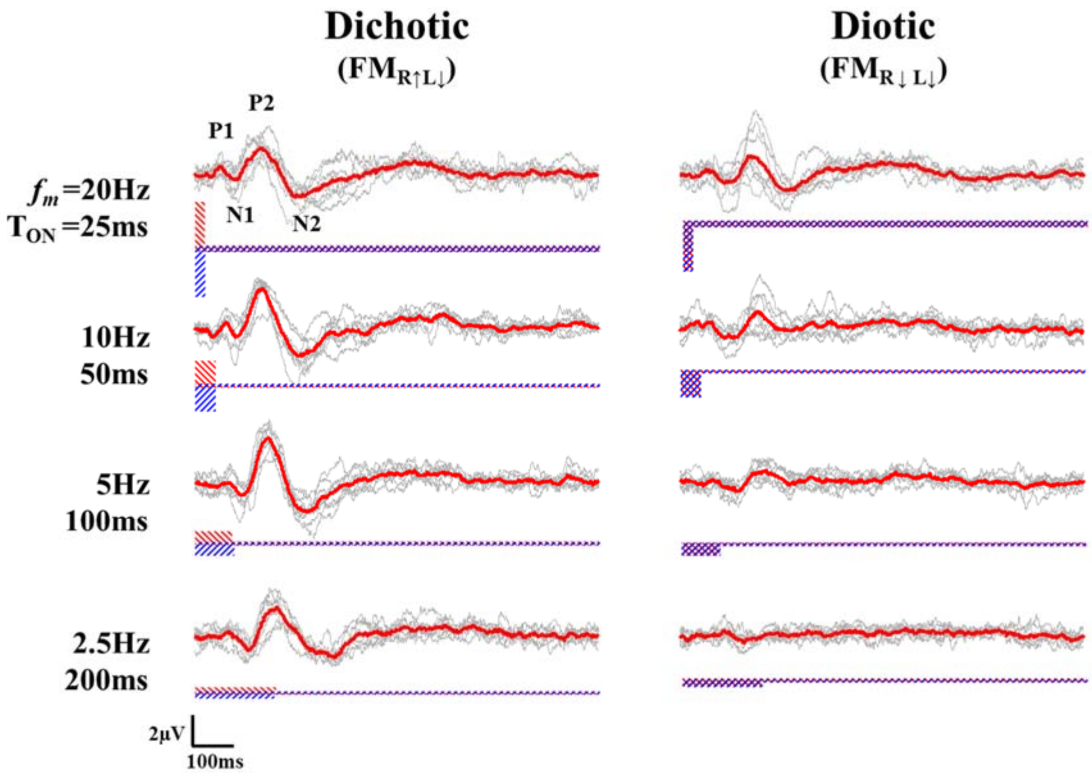

Figure 4-4. AEP responses to a set of f_m/BD configurations and dichotic and diotic stimulation. The responses were grouped by the simulation configuration where BB was $FM_{R\uparrow L\downarrow}$ (left column) and FM was $FM_{R\downarrow L\downarrow}$ (right column) and the f_m / BD (top to bottom). The population average for each condition is shown with a solid red trace and the indivual subject resposnes (N=8) are shown with ligh gray traces. Under the corresponding responses is a visualization of the generated BBs with proportional f_m, BD, and modulation direction.

(6 males and 2 females), ages between 19 and 29 (mean 25). All conditions were recorded in as a single block consisting of at least 512 accepted sweeps. The f_c used in the study was 400 Hz, the BOI was 1.0s, and the stimulus intensity was 75 dBSPL.

The individual subject responses and the population averages, shown in Figure 4-4 were grouped by the modulation frequency (top to bottom) and the stimulation conditions (left and right columns). Underneath each population and average was the corresponding representation of the frequency envelope that shows the duration of the beat and the modulation frequency.

The $FM_{R\uparrow L\downarrow}$ showed an increase in the AEP amplitudes with decreasing f_m from 20 Hz to 5 Hz f_m and a decrease in amplitudes from 5 Hz to 2.5Hz. Furthermore, a dilation of the peak N2 was observed at 2.5 Hz f_m. The peak P1 loses definition as the f_m decreases while the remainder of the peaks remain consistent.

The $FM_{R\downarrow L\downarrow}$ showed a considerable reduction of the AEP amplitudes from 20 to 5

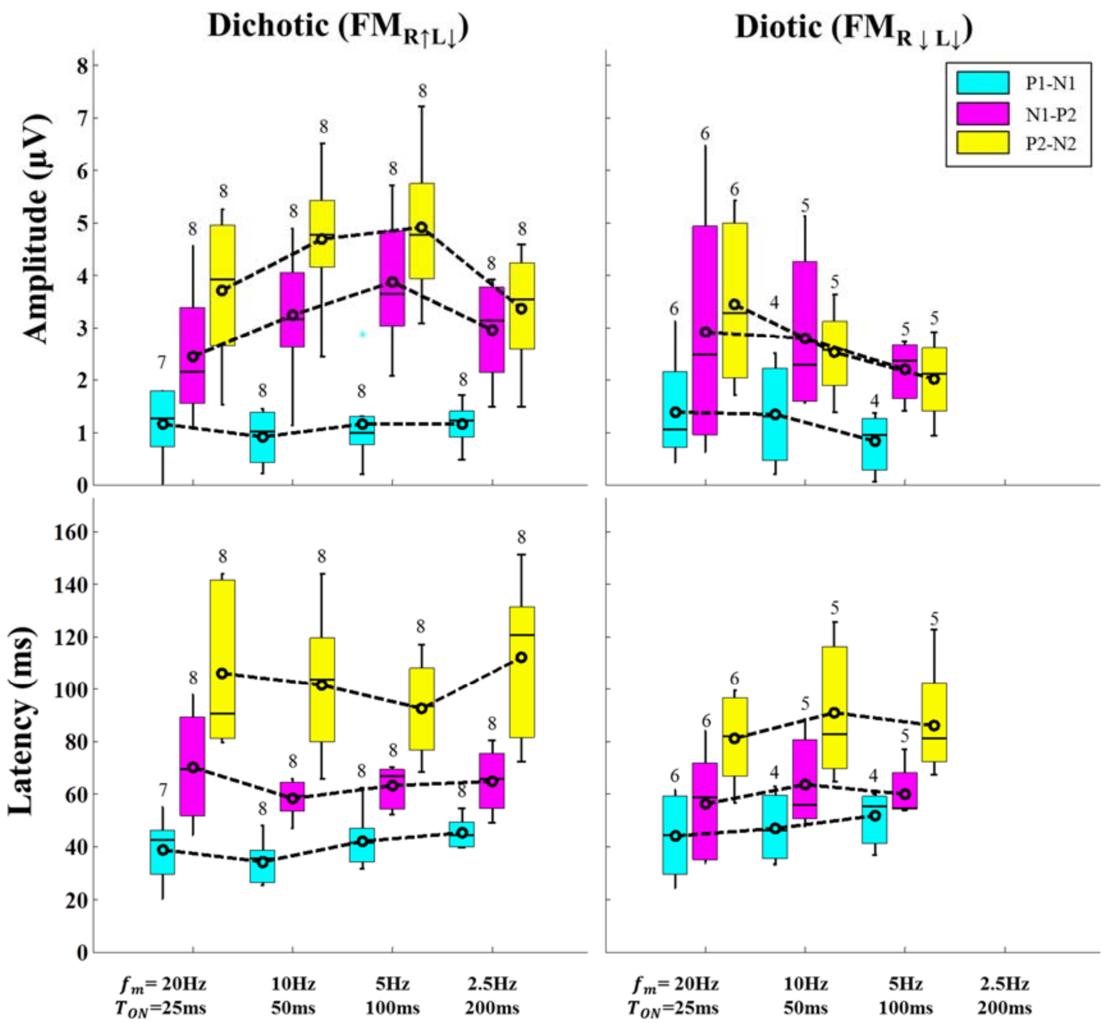

Figure 4-5 Box and whisker plots of the inter-peak amplitude and latency measurements from the modulation frequency study. All subjects elicited detecable peaks from the dichotic stimulation, with the exception of one subject, who did not have a detectable P1 peak at f_m of 20Hz. The number of detecatble peaks varided by condition for the dichotic stimulation. Furthermore, none of the subjects elicited any detectable peaks at f_m of 2.5Hz with the dichotic configuration.

Hz f_m and an absence of detectable AEPs at 2.5 Hz f_m. Furthermore, an average latency increase of 12 ms in was measured between consecutive, decreasing, modulation frequencies across all four peaks in the $FM_{R\uparrow L\downarrow}$ configuration and around 9 ms in the $FM_{R\downarrow L\downarrow}$ configuration.

The $FM_{R\uparrow L\downarrow}$ was capable of eliciting AEPs in almost all cases, with the exception of one subject that did not elicit a detectable P1 peak at 20 Hz f_m. In the $FM_{R\downarrow L\downarrow}$ for 20 Hz f_m only 6 subjects elicited detectable responses across all peaks, at 10 Hz and 5 Hz only 5 elicited responses with N1, P2, and N2 and only 4 elicited P1. At 2.5 Hz f_m none of the subjects elicited detectable responses.

Table 4-1 ANOVA summary of the modulation frequency study.
(* $p \leq 0.1$ and ** $p \leq 0.05$).

			$FM_{R\uparrow L\downarrow}$		**$FM_{R\downarrow L\downarrow}$**	
			F[x,y]	**p**	**F[x,y]**	**p**
Amplitudes	**P1-N1**	f_m	0.6331[3,20]	0.6023	1.6133[2,6]	0.2750
		Sub.	4.6094[7,20]	0.0033**	3.8292[5,6]	0.0664*
	N1-P2	f_m	8.9256[3,21]	0.0005**	1.1740[2,8]	0.3572
		Sub.	12.1550[7,21]	0.0000**	4.1896[5,8]	0.0362**
	P2-N2	f_m	7.3726[3,21]	0.0015**	4.7287[2,8]	0.0441**
		Sub.	6.3440[7,21]	0.0004**	1.9405[5,8]	0.1929
Latencies	**P1-N1**	f_m	3.4099[3,20]	0.0375**	0.3808[2,6]	0.6987
		Sub.	3.3017[7,20]	0.0168**	0.6416[5,6]	0.6786
	N1-P2	f_m	1.6915[3,21]	0.1994	0.1851[2,8]	0.8345
		Sub.	2.4299[7,21]	0.0544*	4.3116[5,8]	0.0336**
	P2-N2	f_m	1.7427[3,21]	0.1890	0.9173[2,8]	0.4378
		Sub.	5.2963[7,21]	0.0013**	5.1846[5,8]	0.0204**

Figure 4-5 shows the inter-peak values of N1-P2 and P2-N2 from the $FM_{R\uparrow L\downarrow}$ configuration achieve maxima at 5 Hz f_m, while the value of P1-N1 does not change with the modulation frequency. The $FM_{R\downarrow L\downarrow}$ configuration shows a general downward trend with increasing f_m for N1-P2 and P2-N2, while the value of P1-N1 remains relatively constant.

The inter-peak latencies in general do not change with f_m and remain relatively constant, with the exception of P2-N2 in the $FM_{R\uparrow L\downarrow}$ configuration, in which the latency shows an abrupt increase from 5 to 2.5 Hz f_m (Figure 4-5), which also coincides with the dilation of the peak N2 seen in the bottom left plot of Figure 4-4.

The ANOVA summary in elicited detectable responses.

Table 4-1confirms the observations mentioned above, that the f_m does not affect the amplitude of P1-N1 in both stimulation conditions. Additionally the amplitudes of N1-P2 and P2-N2 are significantly affected by the f_m in the $FM_{R\uparrow L\downarrow}$ configuration while in the $FM_{R\downarrow L\downarrow}$ configuration only P2-N2 was significantly affected. Only the amplitude of P1N1 was affected by the f_m while the remainder did not show any significant correlation to the f_m. In addition to the f_m the subjects showed to have a significant effect on some of the response amplitudes and latencies.

4.3 The Effects of Rate

This study focused on the effect of the rate of presentation of two consecutive beats, or the BOI. A set of BOIs were tested (0.5, 1.0, 1.5, and 3.0s) on 8 young adults, 5 males and 3 females, ages between 20 and 29, mean age of 24, all with normal hearing

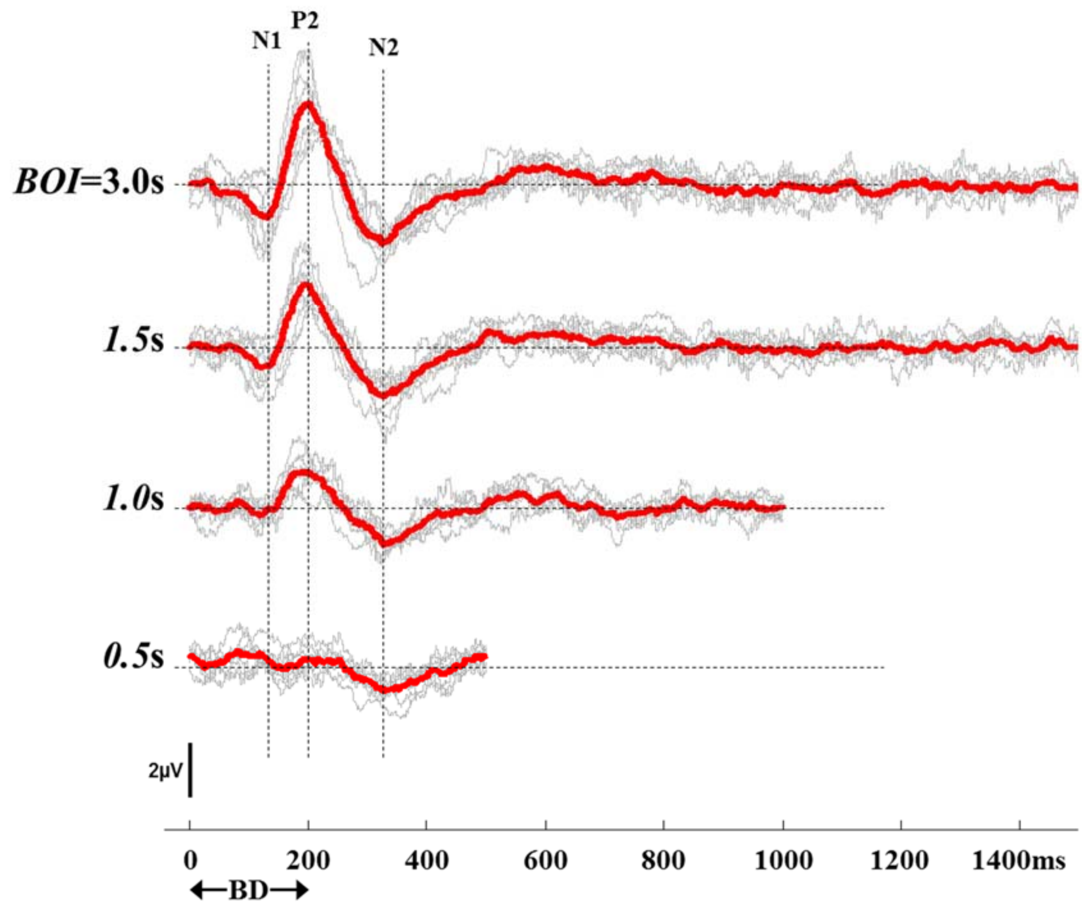

Figure 4-6 AEP responses from several BOI/rates. The responses were grouped by the BOI times with the population averages shown with a solid red trace and the individual subject (N=8) responses with light gray traces. The responses from 3.0 and 1.5s BOI were shortened to 1400ms. The horizontal dashed lines are the zero reference for the corresponding responses and the veritcal dashed lines indicate the latencies of the three major peaks relative to the responses from the 3.0s BOI.

and pure-tone audiometry thresholds below or equal to 25 dBHL. All durations were recorded using an $FM_{R\uparrow L\downarrow}$ configuration all at 75 dBSPL. For each subject and condition the average of the two channels (C_z-A_2 and C_z-A_1) was used for the peak measurements. The differences in amplitude and latency between P2-N2 and P2-N2 were measured and tabulated. The correlation of the response means to the BOI was evaluated using a two-way ANOVA where the main effect was the BOI and the secondary were the subjects.

The population and averaged AEP waveforms are shown in Figure 4-6 from resulting from four different BOI times (top to bottom). The AEP elicited by the 3.0s BOI

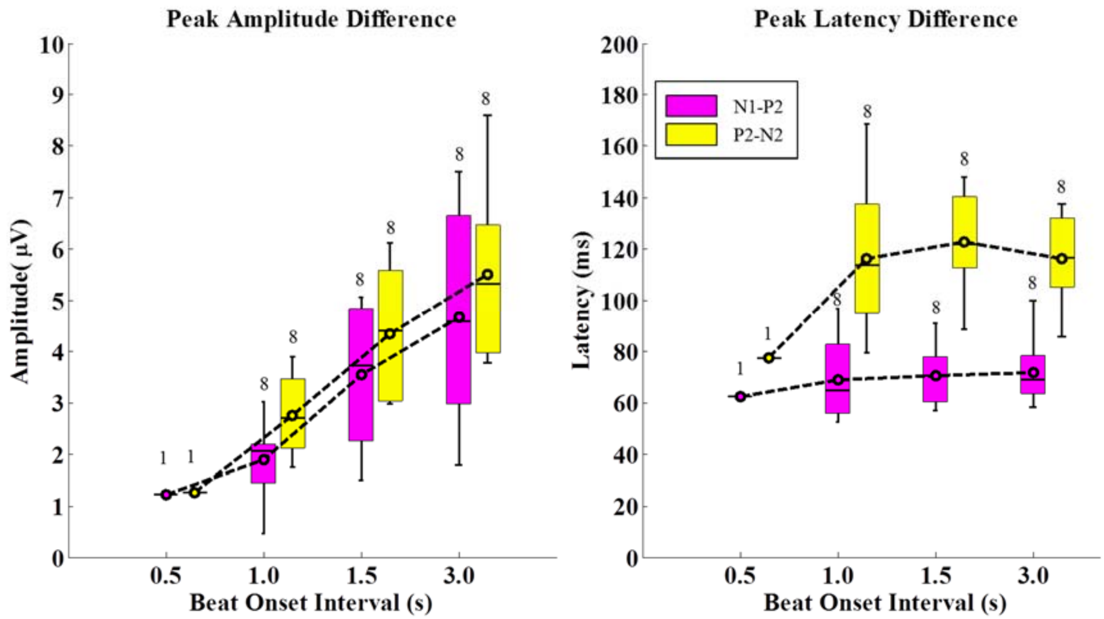

Figure 4-7 Box and whisker plot of the inter-peak amplitudes and latencies from the rate/BOI study. The peak P1 was not consistently present in all subjects and conditions and was removed from the analysis. All subjects elicited detectable peaks for BOI between 1.0 and 3.0s, while only one subjects elicited detectable peaks at BOI of 0.5s. The corresponding mean values are shown with circles connected with a dashed black line.

have large amplitudes with sharp and well defined peaks for all subjects, however, as the BOI decreases the peak amplitudes decrease and loose definition. At BOI of 0.5s a slight negativity with latency corresponding to N2 and the remainder of the peaks diminish. The peak P1 was excluded from the measurements due to inconsistencies in latency of the individual subjects and lack of correlation between the two buffers, so the inter-peak measurements only consisted of N1-P2 and P2-N2.

Figure 4-7 shows a box and whisker plot of the inter-peak amplitudes (left plot) and latencies (right plot) for N1-P2 and P2-N2. The amplitudes in Figure 4-7 show an increase of 3.4 μV for N1-P2 and 4.25 μV of P2-N2 as the BOI increases from 0.5 to 3.0s. The latencies remain relatively constant and unaffected by the BOI. Only one of the subjects elicited responses at BOI of 0.5s, while in the remainder of the cases all subjects elicited detectable responses.

The two-way ANOVA in Table 4-2 excluded the measurements from the 0.5s BOI due to small sample size of one. The ANOVA confirms the observations in Figure 4-7, that a significant correlation exists between the N1-P2 and P2-N2 amplitudes and the BOI. The latencies, on the other hand, did not show any significant correlation to the BOI. The subjects had a significant correlation to both the N1-P2 and P2-N2 amplitudes as well as the P2-N2 latency. The study showed that longer BOI and slower beat rates produce AEP with larger amplitudes and well defined peaks in all subjects.

Table 4-2 ANOVA summary of the BOI/rate study. (* $p \leq 0.1$ and ** $p \leq 0.05$)

			F[x,y]	p
Amplitudes	N1-P2	BOI	21.11[2,14]	0.00^{**}
		Sub.	7.53[7,14]	0.00^{**}
	P2-N2	BOI	25.35[2,14]	0.00^{**}
		Sub.	5.85[7,14]	0.00^{**}
Latencies	N1-P2	BOI	0.11[2,14]	0.90
		Sub.	0.76[7,14]	0.63
	P2-N2	BOI	0.34[2,14]	0.72
		Sub.	2.46[7,14]	0.07^{**}

4.4 The Effects of the Carrier Frequency

This study was used to characterize the effect of the carrier frequency f_c on the responses and to determine if a threshold-like effect is observed similar to the 2T method (Licklider et al. 1950). The study consisted of 7 subjects, 4 males and 3 females, all young adults, ages between 20 and 29 (mean 23) with normal hearing and pure tone audiometry below or equal to 25 dBHL. A set of seven carrier frequencies were used in the study between 250 and 2000 Hz. All frequencies were recorded using the dichotic $FM_{R\uparrow L\downarrow}$ configuration, except 250 Hz was recorded with both the $FM_{R\uparrow L\downarrow}$ and $FM_{R\downarrow L\downarrow}$ configurations to verify that the FMR were not a factor in this case. The intensity in this study was 70 dBHL which is the equivalent of 75 dBSPL at 400 Hz and 70 dBSPL at 1000 Hz.

The waveforms Figure 4-8 show a gradual decrease of the AEP amplitudes as the f_c increases from 250 HZ to 1000 Hz and the AEP responses become undetectable for f_c

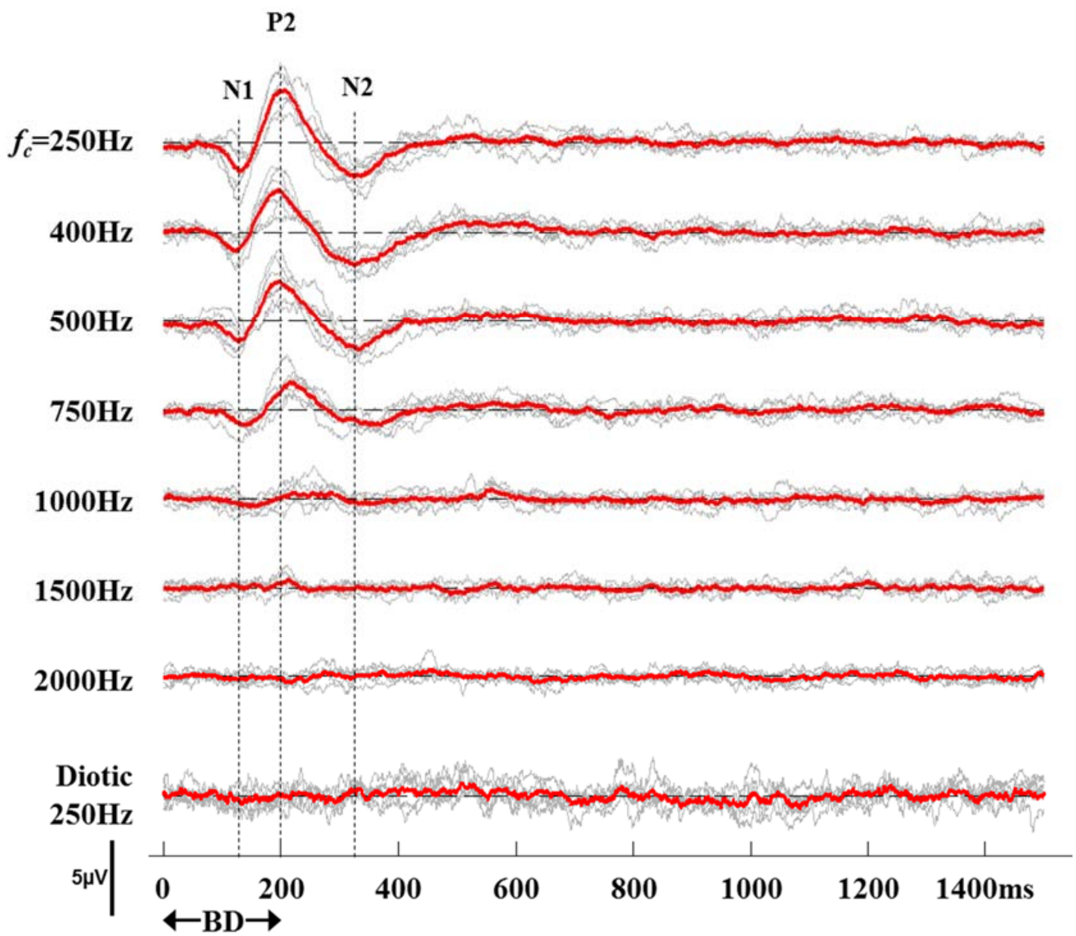

Figure 4-8 AEP responses from several different carrier frequencies. The population averages are shown with a solid red trace while the individual subject (N=7) responses are shown with light gray traces. The horizontal dashed lines indicate the zero point for the corresponding responses. The vertical dashed lines indicate the latencies of the three major peaks relative to the peaks. The beat duration (BD) is shown as a frame of reference at the bottom. The responses shown the bottom plot were recorded using a diotic configuration with only 128sweeps, in order to determine the presence of FM responses from frequencies below 400Hz.

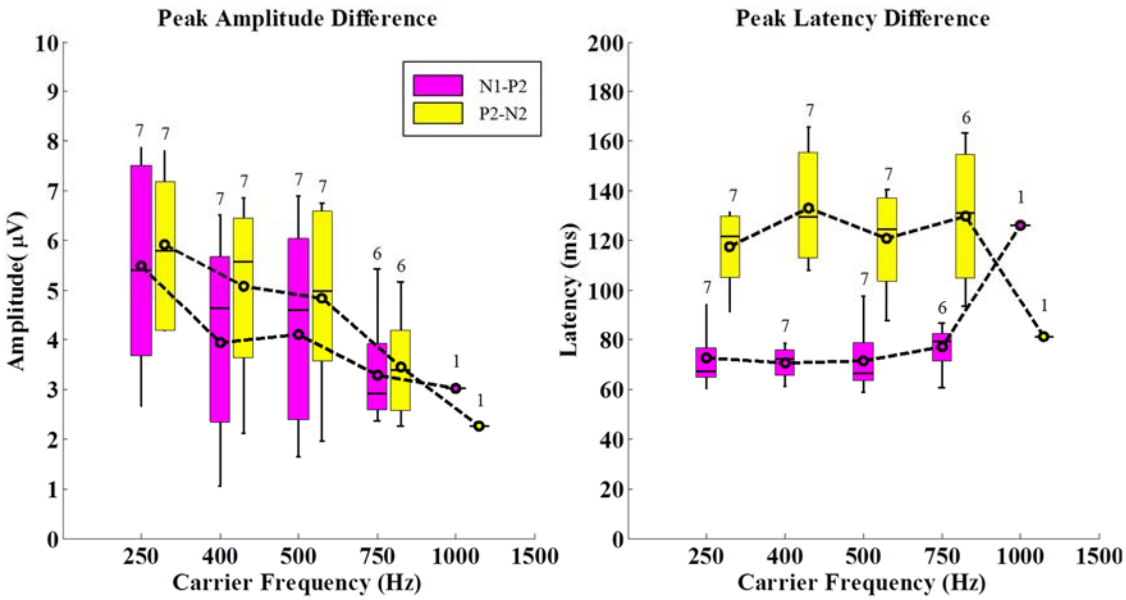

Figure 4-9 Box and whisker plots of the inter-peak amplitudes and latencies from the carrier frequency study. All subjects (7) elicited detectable peaks from 250 to 500Hz, only six subjects at 750Hz, and only one at 1000Hz. None of the subjects elicited detectable peaks at 1500 and 2000Hz. The peak P1 was inconsistent between subjects and conditions and was removed from the analysis. The group averages are shown with circles connected with black dashed lines.

of 1500 and 2000 Hz. Furthermore, the $FM_{R\downarrow L\downarrow}$ at 250 Hz did not elicit any detectable responses indicating that the f_m of 2.5 Hz relative to the f_c of 250 Hz is not large enough to evoke FMR. The AEP show a threshold between 1000 and 1500 Hz where the BBR diminish below the noise levels.

The inter-peak measurements consisted only of N1-P2 and P2-N2 because the peak P1 was inconsistent between subjects and in most cases lacked coherence between the two buffers. From 250 to 500 Hz all subjects elicited detectable responses, at 750 Hz six subject produce detectable responses, at 1000 Hz only one, and 1500 and 2000 Hz none of the subjects produced measurable responses. Figure 4-9 shows a general decrease in response amplitudes as the f_c increases with the maximum amplitudes at 250 Hz. The latencies do not show any trends in regards to the f_c. The latencies, on average, do not show any shifts with respect to the f_c and the amplitudes decrease from 5.50 µV for N1-

P2 and 5.92 μV for P2-N2 to 3.01 μV and 2.76 μV respectively as the f_c increases from 250 to 1000 Hz.

The two-way ANOVA in

Table 4-3 excluded f_C of 1500 and 2000 Hz since none of the subjects produced measurable responses and 1000 Hz due the small sample size. The ANOVA confirmed the observations from Figure 4-9 that a significant correlation exists between f_c and the amplitudes of N1-P2 and P2-N2. Additionally, the ANOVA supported the observation that the latencies of N1-P2 and P2-N2 do not have a significant correlation to f_c. Furthermore, the ANOVA showed correlation between the subjects and the amplitudes of the responses and the latency of P2-N2. The study showed that a threshold exists between 1000 and 1500 Hz where the BBR are no longer produced by the unitary beats.

Table 4-3 ANOVA summary of the carrier frequency study.
(* p≤0.1 and ** p≤0.05)

			F[x,y]	p
Amplitudes	**N1-P2**	f_c	10.75[3,17]	0.00**
		Sub.	16.79[6,17]	0.00**
	P2-N2	f_c	21.45[3,17]	0.00**
		Sub.	17.29[6,17]	0.00**
Latencies	**N1-P2**	f_c	0.43[3,17]	0.73
		Sub.	3.78[6,17]	0.01
	P2-N2	f_c	1.03[3,17]	0.40
		Sub.	1.82[6,17]	0.15

4.5 The Effects of Intensity

This study primarily focused on the effect of the stimulus intensity on the responses. A set of stimulus intensities was used from 25 to 75 dBSPL increments of 10dB. The study consisted of 7 (5 males and 2 females) subjects, all young adults, ages

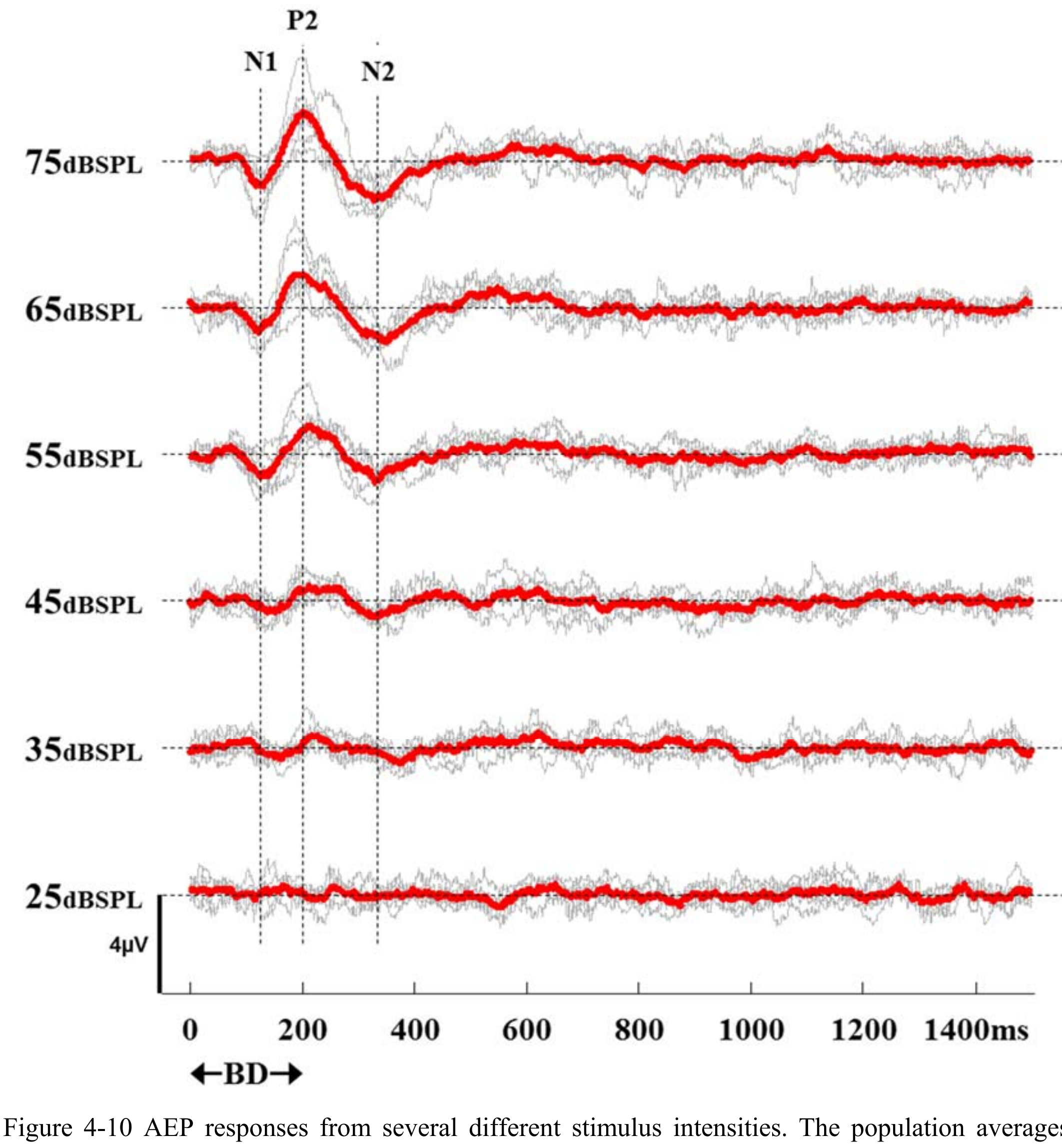

Figure 4-10 AEP responses from several different stimulus intensities. The population averages for each stimulus intensity are shown with a solid red trace while the individual subject (n=7) responses are shown with light gray traces. The horizontal dashed lines indicate the zero reference for the corresponding responses and the vertical dashed lines indicate the latencies of the three major peaks relative to the responses from 75 dBSPL. The beat duration (BD) in shown on the bottom as a frame of reference.

between 20 and 29 (mean 23), with normal hearing and pure-tone audiometry below or equal to 25 dBHL. All of the conditions were recorded using $FM_{R\uparrow L\downarrow}$ configuration with carrier frequency f_c of 400 Hz and modulation frequency f_m of 2.5 Hz.

The AEP responses in

Figure 4-10 show a general gradual decrease in amplitude as the intensity decreases from 75 to 35 dBSPL, while 25 dBSPL the responses diminsih and become udnetectable. On average did not have a substantial shift in latency with respect to the stimulu intensity. The amplitudes decreased from 3.20 μV for N1-P2 and 3.74 μV for P2-N2 at 75 dBSPL to 2.03 μV and 1.75 μV respectively at 45 dBSPL. This equates to and average slope of-0.04 μV/dB for N1-P2 and -0.07 μV/dB for P2-N2.

The peak P1 was excluded from the analysis due to lack of consistency between the subjects, in terms of latency, and lack of correlation between the two buffers. The box and whisker plots in Figure 4-11 show a relatively linear decrease of both the N1-P2 and

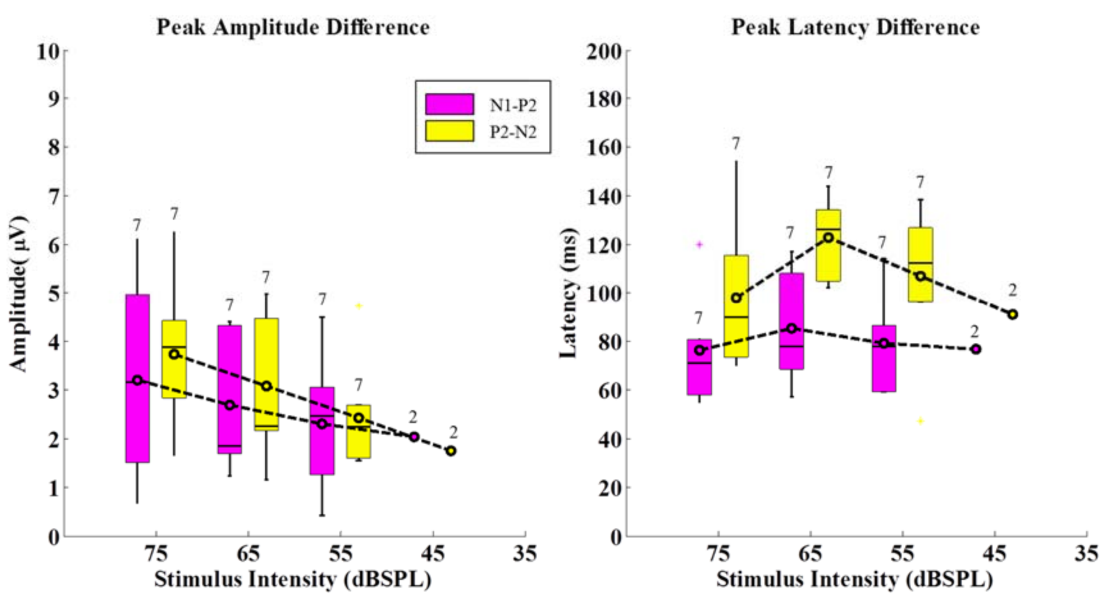

Figure 4-11 Box and whisker plots of the inter-peak amplitudes and latencies from the intensity study. All subjects (7) elicited detectable peaks for intensities from 55 to 75dBSPL, only two subjects elicited detectable peaks at 45dBSPL, and none of the subjects elicited detectable responses for 25 and 35dBSPL. The group means are shown with circles connected by a black dashed line.

P2-N2 amplitudes as the stimulus intensity decreases from 75 to 45 dBSPL. The latencies do not show any apparent trends relating to the stimulus intensity.

The two-way ANOVA in Table 4-4 excluded the intensities of 25 and 35 dBSPL because none of the subjects elicited measurable responses and 45 dBSPL due to the small sample size. The ANOVA confirms the correlation of the N1-P2 and P2-N2 amplitudes to the stimulus intensity. Additionally the ANOVA confirms the lack of correlation between the latencies and the stimulus intensity. Furthermore, the subjects showed a significant effect on the response amplitudes and the latency of P2-N2. The study found an intensity threshold around 45dBSPL at which the beats do not produce any detectable AEP and that there may be a linear correlation of the amplitudes and the stimulus intensity.

Table 4-4 ANOVA summary of the intensity study.
(* $p<0.1$ and ** $p<0.05$)

			F[x,y]	p
Amplitudes	N1-P2	Int.	2.45[2,12]	0.13
		Sub.	10.16[6,12]	0.00**
	P2-N2	Int.	5.52[2,12]	0.02**
		Sub.	8.03[6,12]	0.00**
Latencies	N1-P2	Int.	0.48[2,12]	0.63
		Sub.	2.34[6,12]	0.10*
	P2-N2	Int.	2.68[2,12]	0.11
		Sub.	2.82[6,12]	0.06*

4.6 Psychophysics and Subjective Thresholds

The psychophysics study focused on the ability of the subjects to detect the fluctuation in the presented stimuli using $FM_{R\uparrow L\downarrow}$ (BB) and $FM_{R\downarrow L\downarrow}$ (FM) configurations at different modulation frequencies at different carrier frequencies. The study consisted of 7 young healthy adults (4 males and 3 females), ages between 19 and 29 (mean 24). All subjects had pure-tone audiometry below 25 dBHL and all elicited AEP to the unitary BB.

In certain cases the subjects found it difficult to discriminate between the absence or presence of beats and modulations, for certain frequency combinations. Additionally if consecutive modulation frequencies were presented without changing the carrier frequency, the subjects will lock on to the fluctuations in the stimuli and follow them to the extremes in either direction. This was accounted for by randomizing presentation of the modulation and carrier frequencies.

The subject responses showed that BB had thresholds between 0.5 and 2 Hz and average of 1 Hz which was below the FM threshold of 1 to 5.66 Hz and average of 3.56 Hz for carrier frequencies between 250 and 750 Hz. However, the thresholds crossover around 1000 Hz where the BB range is between 1 and 8 Hz with average of4.83 Hz while the FM is between 2 and 8 Hz with average of 5.26 Hz. For carrier frequencies of 1500 and 2000 Hz the BB thresholds, of 8 to 11.31 Hz with average of 10.84 Hz, are below the FM thresholds, between 2.83 and 11.31 Hz with average of 8.01 Hz.

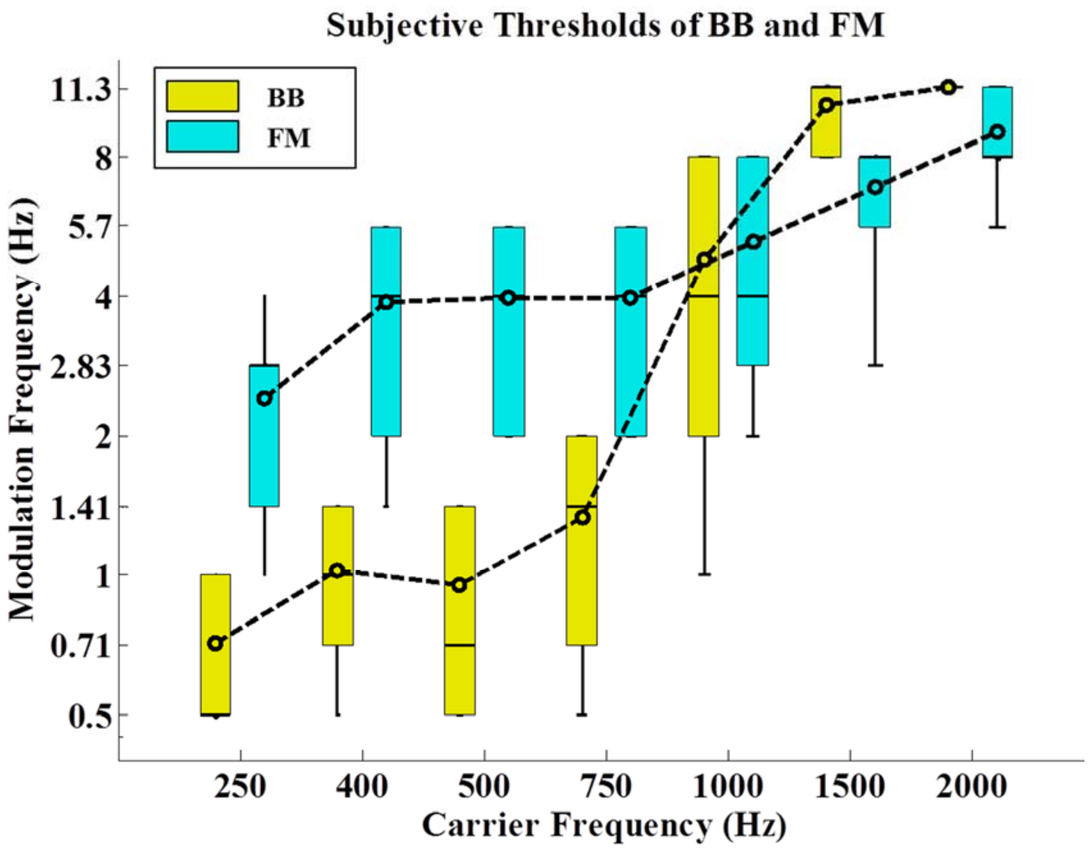

Figure 4-12 Box and whisker plots of the subjective detection thresholds for BBs and FM. The thresholds shown in the figure are the modulation magnitudes f_m values with respect to different carrier frequencies f_c at which the subjects detected any kind of fluctuations or changes in the stimuli. The thresholds were determined using a dichotic BB ($FM_{R\uparrow L\downarrow}$) and diotic FM ($FM_{R\downarrow L\downarrow}$) configurations.

The study showed that for carrier frequencies up to 750 Hz the BB and FM have clearly distinguishable threshold without any overlap. On average the separation, up to 750 Hz f_c, was 2.56 Hz which indicates that any fluctuations in the stimuli perceived below the FM threshold line are in fact BBs.

4.7 Supplemental Studies

In addition to the main five studies two supplemental studies were conducted to cover certain aspects that may have been omitted in the main studies. The first study was used to compare the transient unitary BB responses to SSR responses. For this study three

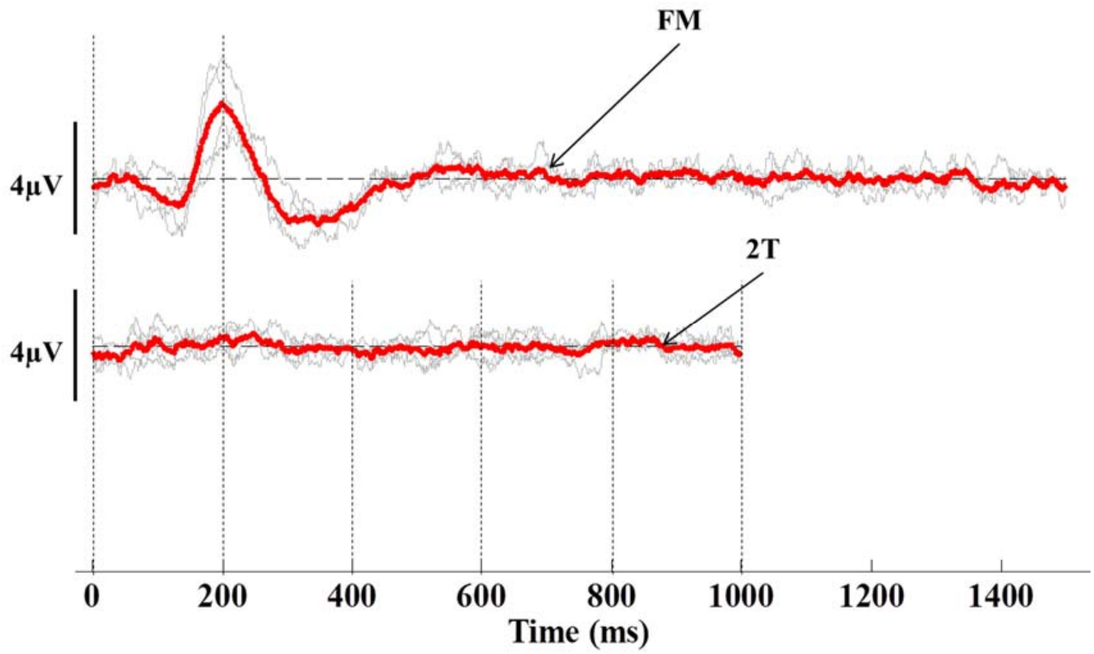

Figure 4-13 AEPs from FM and 2T generated BBs. The two plots show the individual subject (N=5) responses with light gray traces and the population average solid red. The AEPs were generated using the FM method (top) and the 2T (bottom) method. The vertical dashed lines represent the onset of the beats. The FM method only generates one beat while the 2T generates five beats in one second. The top plot shows the typical BBR described previously and the bottom plot does not contain any detectable responses.

recordings were performed on 6subjects (4 males and 2 females), ages between 20 and 29 (mean 25).One recording was with FM BBs with modulation frequency of 2.5 Hz, BD of 200ms, carrier frequency of 400 Hz, and BOI of 1.5s for 512sweeps. The other two recordings were performed using the conventional 2T BB method with 400 Hz (Left) and 405 Hz (Right) pure-tone stimuli, mimicking the 5 Hz difference between 402.5 and 397.5 Hz generated by the FM method during the **ON** portion of the stimuli. The two recordings were performed with 256 sweeps each and with opposite polarities in order to achieve the same phase cancellation as the FM BB method. The results from this study are shown in Figure 4-13 in which the top plot is the unitary beat while on the bottom is the 2T BB. The FM BB evoked the same AEP waveforms as described previously while the 2T method did not evoke any detectable responses.

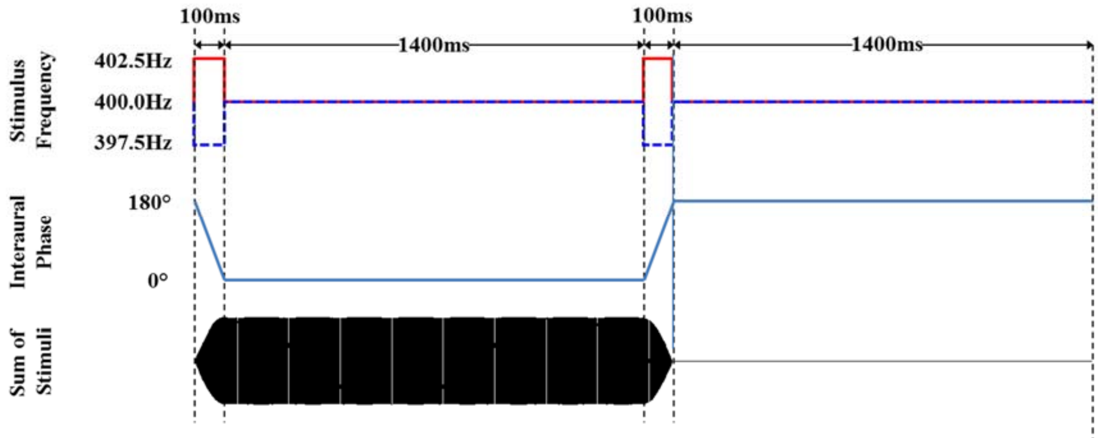

Figure 4-15 Split beat stimulus envelope and stimulus configuration. The T_{ON} segment was halved to 100ms from the original 200ms, while the f_m was kept the same at 2.5Hz. This configuration will produce a binaural phase change from 180º to 0º or vice versa unlike a single beat, in which the binaural phase starts and ends at 0º. The top plot shows the frequency envelopes (right is solid red and left is dashed blue). The middle plot shows the binaural phase that results from the stimuli and the bottom plot shows the sum of the left and right sounds stimuli.

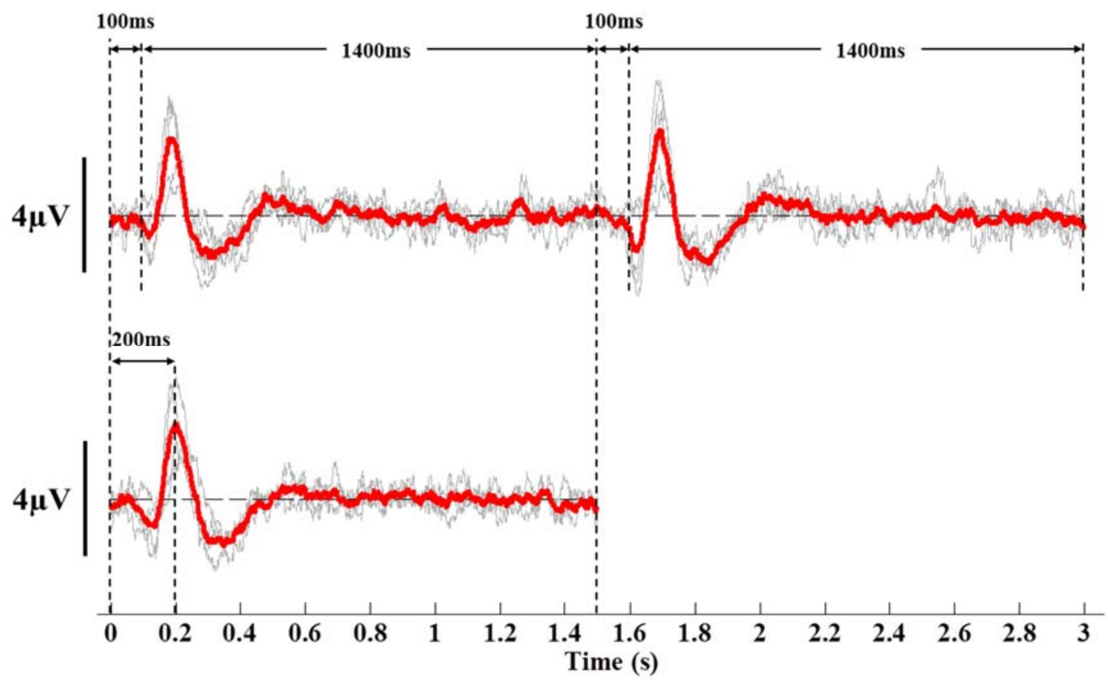

Figure 4-14. Population and averages AEP from the phase study. The figure shows the population (N=6, gray) and the average (red) AEP from the split beat (top) and the full FM beat (bottom). The vertical dashed lines show the event times, in the top plot each event is only 100ms and in the bottom the event is 200ms. The split beat evoked AEP with the same characteristics as the full beat with slight amplitude differences. The first AEP evoked by the split beat has generally smaller amplitudes than the second.

The beats generated using FM stimuli can be described as two transient phase events. The first event is the transition from 180º to 0º binaural phase difference or the first 100 ms of the BD. The second event is the transition from 180º back to 0º or the second 100 ms of the BD. The second supplemental study was an attempt to separate the two phase events into individual transient events, or split beat, and observe the resultant responses. The stimuli used in the study were generated in a similar manner as the ones described previously. The first difference in the generation process was the BD (T_{ON}) was not calculated per Equation 3-12 but rather $T_{ON} = 1/4f_m$, which is the equivalent to half of the BD. The second difference was that two **ON** segments were used during the duration of a single stimulus, one at the beginning and the second half way through the stimulus, shown in the top plot of Figure 4-15. The first **ON** segment generates the first phase event, which shifts the binaural phase from 180º to 0º. The second **ON** segment shifts the binaural phase difference from 0º to 180º. After each **ON** segments is an **OFF** segment with duration of 1400ms. This provides enough time for the AEP to diminish naturally and avoid any responses overlap. This configuration yields two stimuli that start at a binaural phase difference of 180º, 100 ms later shift to 0º difference, remain in this state for 1400ms, then in 100 ms shift from 0º to 180º difference, and remain in this state for 1400ms, shown in the middle plot of Figure 4-15. The stimuli can be delivered continuously without any interruptions.

The same set of subjects mentioned in the first supplemental study was used in the second supplemental study. Figure 4-14 show the resultant AEP from this study, the top waveform was generated using the split beat method and the bottom waveform was generated using the full beat method. The AEP of the two methods have similar post onset latencies of the peaks even though the BD was halved and with small differences in peak amplitudes. During the **OFF** segments the stimuli did not produce any responses. The second shift at 1400 ms of the split beat produced AEP with larger amplitudes relative to the one a 0 ms.

Chapter 5.
DISCUSSIONS AND SUMMARY

5.1 Discussion

BB generated using FM stimuli are a novel concept which has not been investigated. The five studies discussed in this dissertation were used as a systematic approach to characterize the responses evoked by this method. The studies focused on four key stimulus parameters, the modulation frequency, carrier frequency, BOI, and the stimulus intensity. These parameters can be closely related to the conventional 2T method. The carrier frequency and stimulus intensity are equivalent in both methods, the modulation frequency can be related to the frequency difference between the two sounds, and the BOI can be related to the beating frequency. Characterizing the behavior of the responses with respect to the four stimulus parameters should provide a general, working baseline for FM elicited BB.

The FM used in the stimuli has been shown to evoke AEPs or ERPs (Dimitrijevic et al. 2008), so it was essential to characterize the effect that the FM has on the responses and determine if it possible to generate only BBR without the presence of FMRs. As mentioned previously the FM method evokes BCR, which are a combination of BBR and FMR and the first study focused on the FM and FMR. In their study (Dimitrijevic et al. 2008) showed that if the modulation magnitude is small enough it will not elicit any measurable responses. The same applies in the case of the FM elicited BBs, if the stimulus modulation frequency is small enough relative to the carrier frequency the FMR elicited should be negligible compared to the BBRs. The results from the modulation frequency study showed that BBR and FMR are similar in morphology indicating that they are nonlinear and cannot be separated from each other by linear subtraction. The study showed that decreasing the modulation frequency also decreases the FMR while preserving the BBR, indicating that in fact it is possible to elicit only BBR using the FM method (Figure 4-4).

The carrier frequency is equivalent in both the 2T and FM methods, and can be directly correlated between the two. The second study focusing on the carrier and frequency showed that a frequency threshold exists up to which AEP can be evoked and subjectively perceived. The results from the study showed a threshold, around 1000 Hz, above which the responses diminish significantly. This finding coincides with other studies (Licklider et al. 1950, Garner and Wertheimer 1951, Zwislocki and Feldman 1956, Ross et al. 2007, Schiano et al. 1986) which subjectively determined that the range of 1100 to 1300 Hz is the threshold up to which sounds can be localized using temporal differences and incidentally BB can be perceived. The ITD and IPD sensitive neurons are utilized primarily in sound localization on the horizontal plane and may be involved in the perception of BBs.

The IPD and ITD neurons are predominantly innervated by low frequency neurons, which are capable of encoding the phase (phase locking or FFR) of the frequency they carry which in turn is limited by the maximum firing rate of that particular neuron. Typically, FFR neurons can phase lock to frequencies lower than 1000 Hz (Batra et al. 1986), which accounts for the abovementioned thresholds for BBs and temporal location cues. Since the generation of BBs primarily relies on IPD it is also constrained by the threshold.

Another aspect that was covered in the carrier frequency was that the modulation frequency of 2.5 Hz relative to the carrier, at 250 Hz, is 1%, which is larger than the 0.625% at 400 Hz observed in the modulation frequency study, and may evoke FMRs. However, the $FM_{R\downarrow L\downarrow}$ configuration showed that even though the modulation ratio at 250 Hz was larger than at 400 Hz it did not evoke detectable FMRs in any of the subjects.

The intensity study showed that the stimulus intensity has a significant effect on the responses amplitudes, and show a threshold between 45-35 dBSPL. Additionally, the AEP showed a relatively linear decrease in amplitude with decreasing stimulus intensity. The stimulus intensity may also be a factor that affects the response amplitudes at different carrier frequencies, because the sensitivity of the human ear varies with frequency. Several standards exist, like the ISO226 and ISO389.2, which provide standard sound levels at which humans perceive different frequencies as equal in loudness. The ISO389.2 was used for compensating the loudness of the different frequencies in the carrier frequency study, since it is targets ER-3A inserts, which were used in all of the studies. According to the ISO389.2 standard the correction value (dBSPL to dBHL) is 0db at 1000 Hz, 14db at 250 Hz and 5.5dB at 500 and 400 Hz. Since the difference in intensity between 400 and 250 Hz is 8.5 dBSPL it may be large enough to cause variations in the AEP amplitudes between the two frequencies. The intensity difference may also justify the amplitude maxima at observed at 250 Hz in the carrier frequency study.

One of the greatest advantages of the FM evoked BB over the 2T BBs is that the rate at which the beats occur is independent from the 2T frequency difference. With the 2T method the beat rate is equal to the difference of the two pure tone frequencies and cannot be altered without changing the two frequencies. However, with the FM method the two concepts are completely independent from each other. Since the modulation envelope dictates when the stimulus will modulate it also dictates when the beat will occur. The only constraint is that the maximum beating rate cannot exceed the 2T frequency difference. Slowing down the beating rate is advantageous when investigating LLR, which tend to increase in amplitude with slower rates (Picton 2011). Even though the stimuli are presented continuously, without any amplitude changes, the occurrence of the binaural beat results in event related responses (ERP), which respond to rate in a similar manner as conventional stimuli with SOA. The rate study showed that longer BOI elicited responses with larger amplitudes when compared to short BOIs. Additionally, at a short BOI (0.5s) only one subject elicited measurable responses, indicating that a lower threshold exists for evoking BBR.

The fact that the responses diminish with shorter BOI and faster rates, may be the reason as to why the 2T method is only capable of evoking SSR. In order to achieve slower rates with the 2T method the frequency difference between the two stimuli would have to be decreased, which in turn will decrease the response amplitudes, which can also observed in the modulation frequency study. The first supplemental study showed that with the 2T it is difficult, if not impossible, to evoke large enough responses to be captured and measured without additionally processing and filtering, when using the equivalent parameters as the FM method.

The FM generated BB subjectively were perceived by the subjects as a continuous pure-tone sound with a faint pulsation which occurs at a rate equal to the actual beating rate. Some subject found it difficult to locate the origin of the beat while others perceived it as moving from one side to the other. The individual beats were easier to hear and were more persistent than the ones generated using the 2T method, which after a certain period of time became hard to follow or hear.

The subjective threshold study looked into the modulation frequency thresholds at which BB and FM can be heard for a given carrier frequency. The results of the study showed a cutoff between 750 Hz and 1000 Hz up to which BB can be perceived without perceiving the FM. Between 250 and 750 Hz, carrier frequency, the FM response thresholds were, on average, 2.56 Hz above the BB response threshold, which indicates that the perception of pulsation was due to the interaural phase difference instead of the FM. However, above the 750-1000 Hz cutoff the BB threshold were above the FM thresholds indicating that perceived pulsation is primarily the result of the FM rather than the BB.

The cutoff observed in the subjective study also coincides with the cutoff observed in the carrier frequency study at which the measurable responses diminish. An important conclusion from this is that at low frequencies, below 1000 Hz, the modulation frequency required to generate BB is smaller than the one for FM, since this validates the FM method as a feasible alternative for generating transient AEPs to unitary BB.

All studies showed that the subjects had a significant effect of on the amplitudes of the AEP and in some cases the latencies. This may be due to the nature of the LLR, which tend to vary between subjects and their level of alertness. The effect of the subjects on the response amplitudes may be reduced, or even become insignificant, by increasing the sample size.

The second supplemental study may provide more insight on the generators of the AEP observed in the other studies. The study showed that the binaural phase transition from 0º to 180º and vice versa, produced AEP with similar characteristics to the AEP discussed in the remainder of the studies. One theory that can be derived from this study is that a full beat consists of two consecutive binaural phase transitions. However, due to adaptation, the auditory cortex does not have enough time to recover from the AEP generated by the first phase transition of the beat. For the same reason it fails to generate a significantly large response to the second phase transition of the beat. By splitting up the beat, and introducing a long enough delay of 1400 ms the auditory system has enough time to recover and respond to each phase transition individually.

The method described in this dissertation showed sufficient amount of evidence to validate it as an alternative to the 2T method and as a feasible method of generating transient responses to unitary BB. The results of the five studies can be summarized into a set of parameter values that can be used to evoke transient AEP from unitary BB using FM stimuli. These values are: f_c=400 Hz, f_m=2.5 Hz, BD/T_{ON}=200ms, BOI=1.5s, and stimulus intensity of 75 dBSPL. These parameter values will generate consistent and repeatable LLR from most subjects.

5.2 FUTURE DIRECTIONS

The current stimulus design process was restricted to a certain extent in order to expedite the characterization process and focus only on the parameters of interest. However, the parameters that were not discussed in the studies were the polarity difference between the two stimuli and the direction of modulation. The polarity or phase between the two ears was shown, in the second supplemental study, to have an effect on the response amplitudes. More specifically, the response amplitudes were larger when the binaural phase changed from 0º to 180º relative to the converse.

In addition to the binaural polarity, the direction of modulation also may have an effect on the responses. Furthermore, the modulation frequency study only characterized the FM effects on the responses by only using modulation below the carrier frequency. A configuration in which both stimuli can modulate above or below the carrier frequency, but with different magnitudes, can also be used to generate beats. However, with this configuration both modulation magnitudes would have to be verified that neither will evoke FM AEPs.

Another aspect that can be further explored is the time between transient phase events, discussed in the second supplemental study. The responses may show sensitivity to the rate of occurrence of the transient phase event, by decreasing in amplitude with higher rates. This may provide an explanation as to why the individual phase events result in similar responses as the unitary BBs.

The current studies can be further improved by increasing the sample size for each study in order to better characterize the effect of the subjects on the responses. Additionally, the value sets used for each parameter can be further broadened and increased in order to increase the degrees of freedom. The modulation frequency can also be taken further by characterizing modulation magnitudes smaller than 2.5 Hz in order to determine what to lower threshold down to which the beats can be perceived and evoke AEPs.

BBs rely on the fine IPD sensitive centers of the auditory system, which are primarily involved in low frequency sound localization on the horizontal plane. Unitary BBs can be used to examine the function of these centers, with respect to different frequencies. Furthermore, unitary BBs may be used as a diagnostic tool for evaluating central processing disorders.

5.3 SUMMARY

The studies discussed in this dissertation were designed to tackle the three main objectives discussed in the goals section. From all studies a general population average was compiled in order to obtain a representative response waveform from unitary BBs. The responses that were observed in most cases resemble LLR with the latency of the first visible peak (P1) around 75ms. The response waveforms, in most cases, were composed of four peaks (P1, N1, P2, and P2) all with late latencies and amplitudes in the order of several microvolts. The peak P1, however, was not present in all subjects and cases, and was omitted from some of the studies. The remainder of the peaks were present in all subjects, however, not for all parameter values.

As mentioned previously, the intrinsic stimulus FM has been shown to evoke AEPs and when used to generate BBs the FMR are embedded in the BBR. The studies showed that if the modulation frequency is smaller than 2.5 Hz it will not evoke any detectable AEP responses and is not subjectively perceivable. At the same modulation frequency, the unitary BBs still can evoke detectable AEP responses and can be detected subjectively. This confirms that, in fact, it is possible to generate unitary BBs that will not evoke any substantial FM responses while still evoking unitary BB responses. The same was confirmed subjectively.

To summarize all of the study results, the method discussed is capable of generating unitary BBs which can be used to evoke transient AEPs. The behavior of the carrier frequency can be equated to the 2T thresholds for the base frequency, more specifically the upper threshold between 1000 to 1500 Hz up to which BBs can be detected, both psychophysically and can evoke AEPs. While the FM magnitude can be related to the BFD in the 2T method and similar threshold will apply. The studies, however, did not focus on the upper limit of the BFD, but rather on the reduction of the FM responses.

The BOI showed to have a key role in evoking transient AEPs from unitary BBs. By increasing the time period between BBs increases the magnitude of the evoked responses, which may also justify as to why the 2T method does not evoke large steady state responses. The BOI / rate study showed that a correlation of the responses to the BOI exists and the responses diminish with shorter BOI.

To goal from all studies was to obtain a set of parameter values that will produce unitary BBs capable of evoking transient AEPs with large amplitudes from most subjects, in a relatively short amount of recording time. Based on the stimulation configuration, described in this dissertation, a modulation frequency magnitude (f_m) of 2.5 Hz is capable of evoking unitary BB transient responses without any substantial FM responses.

The necessary beat duration (BD) needed to achieve a 2.5 Hz f_m is 200ms. The BOI should not be smaller than 1.0 s, however the optimal BOI found was 1.5 s, since it produces responses with larger amplitudes relative to a BOI of 1.0 s and requires half of the time to record relative to the BOI of 3.0s. The carrier frequency f_c was not restricted to a single value and can range up to 750 Hz. Larger f_c values than 750 Hz will not result in consistent AEPs and will not evoke responses from all subjects. Furthermore, larger f_c values may require a proportionally larger f_m in order to achieve an equivalent f_m to f_c ratio. The stimulus intensity of 75 dBSPL is within the safe range for noise exposure and is sufficient to produce consistent responses. The intensity, however may need to be adjusted to accommodate hearing levels, either population or subjective, for different f_c since the intensity has a linear correlation to the evoked responses amplitudes.

Overall, the study outcomes fulfilled the stated goals, in that the FM method is capable of evoking transient AEP from pure-tone unitary BBs reliably and repeatedly.

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APPENDIX

A. Matlab Code

Below is the function used to generate the FM stimuli in Matlab. The parameters must be preconfigured in order to obtain the correct waveform that can be used to generate BBs. The input parameters, in sequential order, are: carrier frequency (Hz), modulation frequency (Hz), stimulus sampling frequency (Hz), the duration of the beats (ms), the total length of the stimulus (ms), the sequence of times (ms) at which the beats should occur, and the stimulus polarity (1 or -1). The function outputs the waveform and the envelope used to generate the waveform. The function first converts the sequence of beat onset times to discrete samples using the sampling frequency. The function then generates a blank envelope, filled with zeros, with length equal to the total length of the stimulus, in samples and an envelope for the duration of the beat filled with ones. Next the blank envelope is filled with the beat envelope at each occurrence defined in the sequence. After completing the envelope, the function calculates the phase for each sample in the envelope using Equation 3-9. The value of the first sample is subtracted from the entire phase array so that the waveform always begins with a value of zero. The last step is to generate the waveform by calculating the sine of the phase and multiplying by the polarity value.

```
function [y, env] = generate_waveform(fc,fm,fs,bd,len,seq,pol)
%
% [y, env] = generate_waveform(fc,fm,fs,bd,len,seq,pol)
%
% y     - Generated Waveform
% env   - The envelopes used to generate the stimuli
%
% fc    - Carrier Frequency (Hz)
% fm    - Modulation Frequency (Hz)
% fs    - Sampling Frequency
% bd    - Beat Duration (ms)
% len   - Total Waveform Length (ms)
% seq   - Beat Onset Sequence (array of ms times)
% pol   - Waveform Polarity (1 or -1)
%
% Written by Todor Mihajloski
% University of Miami
%

seq = (seq/1000)*fs+1; % Convert the onset times to samples

env = zeros(1,round(len*fs/1000)); % Generate a blank envelope
beat = ones(1,round(bd*fs/1000)); % Beat segment

for m = 1:length(seq)
    env(seq(m):length(beat)) = beat; % Fill the beat segments
end
theta = cumsum(2*pi*(fc+fm*env))/fs; % Generate the angle array
theta = theta - theta(1); % Start at 0rad
y = pol*sin(theta); % generate the waveform
```

B. Generation of the Standard Response Waveform

The general response waveform shown in Figure 4-1 was generated by combining and averaging the AEPs from several studies and subjects. The AEPs used in the waveforms were chosen based on the quality and amplitudes of the responses. From the modulation frequency study (discussed in Section 4.2) only the responses from the dichotic stimulation were used since they produced AEPs consistently with large amplitudes. From the rate study (Section 4.3) the responses from BOIs of 1.0 to 3.0s were used, from the carrier frequency study (Section 4.4) the responses from carrier frequencies between 250 and 750Hz were used, and from the intensity study (Section 4.5) only the responses from intensities of 55 to 75 dBSPL were used. The left and right channels were averaged together for all subjects. The final combination consisted of a total of 105 individual subject responses from 12 subjects (8 males). The combination of the stimulus parameters consisted of: f_m/BD of 2.5Hz/200ms, 5Hz/100ms, 10Hz/50ms, and 20Hz/25ms; f_c of 250Hz, 400HZ, 500Hz, and 750Hz; BOI times of 1.0s, 1.5s, and 3.0s; stimulus intensities of 55 dBSPL, 65 dBSPL, and 75 dBSPL.

All responses were reduced to 800ms and averaged together to generate the raw and unprocessed population average (top plot in Figure B-1). The responses waveform showed large and sharp P1, N1, P2, and N2 peaks and it is common practice to low-pass filter the waveform in order to obtain a standard response that will fit most cases. However, the cutoff frequency required to reduce the noise in the second half of the response waveform, would have reduced the amplitudes persistence of the four major peaks. The red plots in Figure B-1 show the filtered response waveforms with a 2nd order

Butterworth low-pass filter, with cutoff frequencies at 30Hz (left) and 5Hz (right). The 30Hz cutoff sufficiently reduces the noise in the first half of the response, but not in the second. On the other hand, the 5Hz cutoff reduces the noise in the second half, but also reduces the amplitudes of P2 and N2 peaks, and eliminates the P1 and N1 peaks. The two filtered waveforms were combined together using cross over envelopes, which when combined, result in a waveform that starts with a filter of 30Hz and gradually, over the duration of the response, crosses over to a 5Hz low-pass filter. This allows the high frequency content to be preserved in the first half of the response waveform.

The cross over envelope used for the 30Hz cutoff had a slope of -1 over 800ms starting at 1, while the slope of the 5Hz cutoff was 1 over 800ms and starting at 0. The sum of both envelopes over the duration of the waveform was equal to 1.This approach produces a standard waveform that can be used to characterize the transient AEPs by unitary BBs.

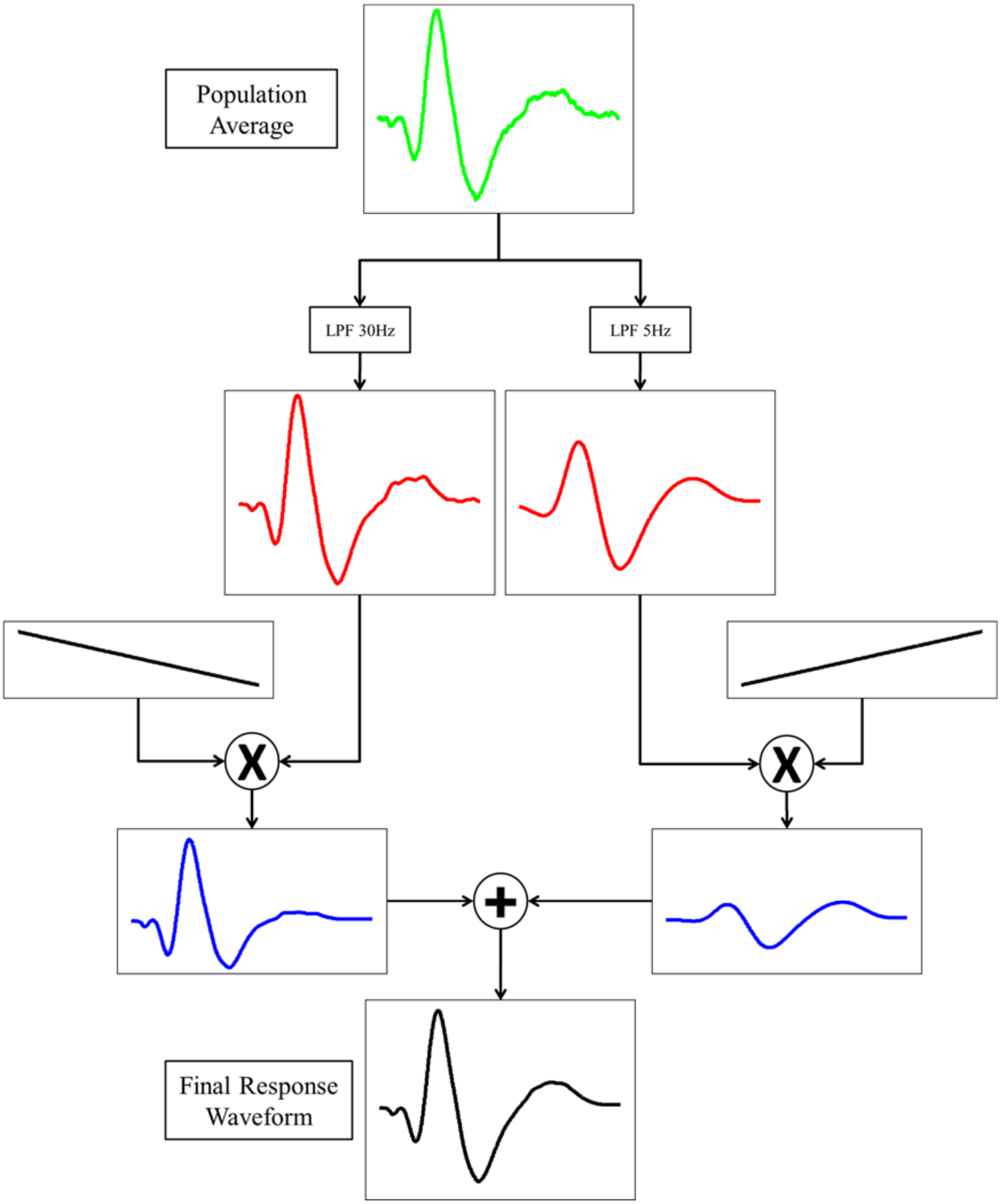

Figure B-1 Diagram illustrating the filter process used for the generation of the general population AEPs. The top plot (green) is the unfiltered population average. The population average is then filtered using low-pass filters with cutoff frequencies at 30 (left branch) and 5Hz (right branch). The filtered signals were then multiplied with envelopes with linear slopes ranging from 1 to 0 (left) and 0 to 1 (right) over the duration of the responses. The products are then summed to produce the final filtered and processed general population average.

C. Descriptive Statistics

This section contains the descriptive statistics, for each study, of the inter-peak measurements from the average of the two channels. The box and whisker plots were generated based on the values contained in the following tables. All amplitude units are μV and the latency units are ms.

Table C-1 Descriptive statistics of the rate study

Amplitudes N_1-P_2 and P_2-N_2								
Inter Beat Interval (s)	**N**	**Mean**	**StDev**	**Min**	**Max**	**Median**	**Q1**	**Q3**
0.5	1	1.23	0.00	1.23	1.23	1.23	1.23	1.23
1.0	8	1.89	0.75	0.46	3.02	2.05	1.45	2.20
1.5	8	3.54	1.36	1.50	5.06	3.73	2.26	4.84
3.0	8	4.67	2.15	1.79	7.51	4.59	2.99	6.65
Inter Beat Interval (s)	**N**	**Mean**	**StDev**	**Min**	**Max**	**Median**	**Q1**	**Q3**
0.5	1	1.26	0.00	1.26	1.26	1.26	1.26	1.26
1.0	8	2.75	0.76	1.75	3.90	2.71	2.11	3.46
1.5	8	4.34	1.24	2.97	6.12	4.40	3.03	5.60
3.0	8	5.51	1.63	3.77	8.60	5.33	3.98	6.47
Latencies N_1-P_2 and P_2-N_2								
Inter Beat Interval (s)	**N**	**Mean**	**StDev**	**Min**	**Max**	**Median**	**Q1**	**Q3**
0.5	1	62.40	0.00	62.40	62.40	62.40	62.40	62.40
1.0	8	68.75	15.61	52.60	96.60	65.00	55.65	82.75
1.5	8	70.62	11.16	57.00	91.00	70.50	60.15	77.75
3.0	8	71.98	13.11	58.40	99.80	68.90	63.45	78.50
Inter Beat Interval (s)	**N**	**Mean**	**StDev**	**Min**	**Max**	**Median**	**Q1**	**Q3**
0.5	1	77.40	0.00	77.40	77.40	77.40	77.40	77.40
1.0	8	116.45	28.65	79.40	168.80	113.90	95.05	137.55
1.5	8	123.00	18.98	88.40	148.20	122.20	112.55	140.50
3.0	8	116.55	17.63	85.80	137.80	116.80	105.45	132.25

Table C-2 Descriptive statistics of the frequency study

Amplitudes N_1-P_2 and P_2-N_2

Carrier Frequency (Hz)	N	Mean	StDev	Min	Max	Median	Q1	Q3
250	7	5.50	2.15	2.67	7.87	5.41	3.68	7.52
400	7	3.93	2.00	1.06	6.51	4.64	2.34	5.67
500	7	4.10	1.98	1.65	6.90	4.59	2.38	6.04
750	6	3.28	1.11	2.36	5.42	2.92	2.58	3.91
1000	1	3.01	0.00	3.01	3.01	3.01	3.01	3.01

Carrier Frequency (Hz)	N	Mean	StDev	Min	Max	Median	Q1	Q3
250	7	5.93	1.46	4.19	7.80	5.80	4.19	7.18
400	7	5.09	1.68	2.12	6.86	5.58	3.62	6.46
500	7	4.83	1.67	1.95	6.76	4.98	3.57	6.59
750	6	3.45	1.01	2.26	5.16	3.37	2.56	4.17
1000	1	2.26	0.00	2.26	2.26	2.26	2.26	2.26

Latencies N_1-P_2 and P_2-N_2

Carrier Frequency (Hz)	N	Mean	StDev	Min	Max	Median	Q1	Q3
250	7	72.43	11.22	60.40	94.00	67.40	65.00	76.80
400	7	70.51	5.97	61.20	78.40	72.00	65.60	75.80
500	7	71.51	12.96	58.80	97.40	66.60	63.80	78.60
750	6	76.90	8.88	60.60	86.40	79.20	71.25	82.50
1000	1	126.20	0.00	126.20	126.20	126.20	126.20	126.20

Carrier Frequency (Hz)	N	Mean	StDev	Min	Max	Median	Q1	Q3
250	7	117.46	14.95	91.40	131.60	121.60	105.20	130.00
400	7	133.26	21.10	108.00	166.00	129.60	113.00	155.80
500	7	120.91	19.24	87.60	140.60	124.40	103.80	137.40
750	6	129.87	28.65	93.60	163.40	130.90	104.85	154.70
1000	1	81.00	0.00	81.00	81.00	81.00	81.00	81.00

Table C-3 Descriptive statistics of the intensity study

Amplitudes N_1-P_2 and P_2-N_2

Intensity (dBHL)	N	Mean	StDev	Min	Max	Median	Q1	Q3
75	7	3.20	1.87	0.69	6.10	3.16	1.51	4.97
65	7	2.69	1.36	1.24	4.40	1.85	1.68	4.32
55	7	2.30	1.32	0.42	4.49	2.46	1.26	3.05
45	2	2.03	0.06	*	*	2.03	*	*

Intensity (dBHL)	N	Mean	StDev	Min	Max	Median	Q1	Q3
75	7	3.74	1.47	1.66	6.24	3.87	2.83	4.42
65	7	3.09	1.48	1.15	4.98	2.25	2.16	4.46
55	7	2.41	1.10	1.54	2.70	2.24	1.61	2.70
45	2	1.75	0.09	*	*	1.75	*	*

Latencies N_1-P_2 and P_2-N_2

Intensity (dBHL)	N	Mean	StDev	Min	Max	Median	Q1	Q3
75	7	76.26	21.54	55.20	80.60	71.00	58.00	80.60
65	7	85.09	21.64	57.00	117.00	77.80	68.60	108.20
55	7	79.06	18.84	59.00	114.20	77.80	59.00	86.40
45	2	76.50	3.82	*	*	76.50	*	*

Intensity (dBHL)	N	Mean	StDev	Min	Max	Median	Q1	Q3
75	7	97.77	29.11	70.20	154.60	89.80	73.60	115.60
65	7	122.77	15.67	102.20	144.20	126.00	105.00	134.20
55	7	107.09	30.32	96.20	138.40	112.20	96.20	127.00
45	2	90.80	16.97	*	*	90.80	*	*

Table C-4 Descriptive statistics of the modulation frequency study – dichotic stimulation

	Amplitudes P1-N1, N_1-P_2 and P_2-N_2								Latencies P1-N1, N_1-P_2 and P_2-N_2							
Modulation Frequency (Hz)	**N**	**Mean**	**StDev**	**Min**	**Max**	**Median**	**Q1**	**Q3**	**N**	**Mean**	**StDev**	**Min**	**Max**	**Median**	**Q1**	**Q3**
20	7	1.16	0.68	0.01	1.79	1.25	0.73	1.78	7	38.46	11.73	20.4	55	42.4	29.8	46.2
10	8	0.9	0.51	0.21	1.44	1.01	0.43	1.38	8	34.35	7.77	25.6	48.2	35.2	26.5	38.85
5	8	1.16	0.78	0.19	1.3	0.98	0.76	1.3	8	42.13	9.85	31.8	62.4	41.4	33.95	46.85
2.5	8	1.16	0.38	0.47	1.7	1.21	0.9	1.41	8	45	5.4	39.4	54.8	44.3	40.05	49.25
Modulation Frequency (Hz)	**N**	**Mean**	**StDev**	**Min**	**Max**	**Median**	**Q1**	**Q3**	**N**	**Mean**	**StDev**	**Min**	**Max**	**Median**	**Q1**	**Q3**
20	8	2.44	1.18	1.08	4.57	2.16	1.55	3.39	8	70.13	19.41	44.4	97.8	69.4	51.65	89.55
10	8	3.23	1.14	1.13	4.89	3.17	2.62	4.06	8	58.45	6.4	47	65.8	59.3	53.5	64.55
5	8	3.87	1.19	2.08	5.71	3.65	3.03	4.86	8	63	7.7	52	70.2	66.9	54.15	69.35
2.5	8	2.95	0.87	1.48	3.91	3.14	2.13	3.77	8	64.9	11.08	48.8	80.4	65.7	54.5	75.45
Modulation Frequency (Hz)	**N**	**Mean**	**StDev**	**Min**	**Max**	**Median**	**Q1**	**Q3**	**N**	**Mean**	**StDev**	**Min**	**Max**	**Median**	**Q1**	**Q3**
20	8	3.72	1.29	1.52	5.26	3.91	2.65	4.95	8	106.05	29.6	79.4	144.2	90.6	81.3	141.9
10	8	4.69	1.2	2.44	6.51	4.77	4.15	5.43	8	101.72	25.36	65.6	144.2	103.7	79.95	119.5
5	8	4.93	1.28	3.07	7.22	4.77	3.94	5.75	8	92.52	17.36	68.6	117	93.6	76.55	108.3
2.5	8	3.36	1.03	1.48	4.59	3.55	2.58	4.24	8	112.25	28.21	72.2	151.6	120.7	81.7	1

Table C-5 Descriptive statistics of the modulation frequency study – diotic stimulation

Amplitudes P1-N1, N_1-P_2 and P_2-N_2									**Latencies P1-N1, N_1-P_2 and P_2-N_2**							
Modulation Frequency (Hz)	**N**	**Mean**	**StDev**	**Min**	**Max**	**Median**	**Q1**	**Q3**	**N**	**Mean**	**StDev**	**Min**	**Max**	**Median**	**Q1**	**Q3**
20	6	1.38	0.98	0.42	3.11	1.04	0.70	2.16	6	44.10	15.26	24.40	61.60	44.40	29.80	59.05
10	4	1.33	0.94	0.20	2.51	1.31	0.47	2.22	4	47.00	12.61	33.20	62.80	46.00	35.35	59.65
5	4	0.83	0.55	0.06	1.36	0.95	0.28	1.26	4	51.85	10.33	36.80	60.00	55.30	41.10	59.15
Modulation Frequency (Hz)	**N**	**Mean**	**StDev**	**Min**	**Max**	**Median**	**Q1**	**Q3**	**N**	**Mean**	**StDev**	**Min**	**Max**	**Median**	**Q1**	**Q3**
20	6	2.92	2.32	0.62	6.48	2.48	0.94	4.93	6	56.40	19.37	33.80	84.20	58.70	35.00	71.75
10	5	2.79	1.50	1.55	5.12	2.28	1.58	4.27	5	63.80	16.74	47.80	88.60	56.00	50.70	80.80
5	5	2.20	0.55	1.39	2.72	2.36	1.64	2.67	5	59.96	9.80	53.80	77.00	54.80	54.20	68.30
Modulation Frequency (Hz)	**N**	**Mean**	**StDev**	**Min**	**Max**	**Median**	**Q1**	**Q3**	**N**	**Mean**	**StDev**	**Min**	**Max**	**Median**	**Q1**	**Q3**
20	6	3.45	1.48	1.71	5.42	3.28	2.03	5.00	6	81.00	16.06	56.80	99.60	81.80	67.00	96.60
10	5	2.52	0.80	1.39	3.62	2.56	1.89	3.13	5	91.04	24.88	64.80	125.60	82.80	69.80	116.40
5	5	2.02	0.72	0.93	2.91	2.11	1.40	2.61	5	86.04	21.46	67.20	123.00	81.00	72.20	102.40

D. ANOVA

This section contains the detailed ANOVA from each study. The two-way ANOVA was used in order to observe the effect of the subjects on the responses in addition to the effect of the main condition. The inter-peak measurements were performed on the average of the two recorded channels.

Table D-1 ANOVA of the modulation frequency study – dichotic stimulation.

Amplitudes P1-N1					**Latencies P1-N1**				
Source	**SS**	**df**	**F**	**p**	**Source**	**SS**	**df**	**F**	**p**
Cond.	0.36	3	0.63	0.6	Cond.	505.91	3	3.41	0.04
Sub.	6.03	7	4.61	0	Sub.	1143	7	3.3	0.02
Error	3.74	20			Error	989.11	20		
Total	10.17	30			Total	2640.25	30		
Amplitudes P2-N1					**Latencies N1-P2**				
Source	**SS**	**df**	**F**	**p**	**Source**	**SS**	**df**	**F**	**p**
Cond.	8.59	3	8.93	0	Cond.	560.57	3	1.69	0.2
Sub.	27.3	7	12.16	0	Sub.	1879.02	7	2.43	0.05
Error	6.74	21			Error	2319.84	21		
Total	42.63	31			Total	4759.43	31		
Amplitudes P2-N2					**Latencies P2-N2**				
Source	**SS**	**df**	**F**	**p**	**Source**	**SS**	**df**	**F**	**p**
Cond.	13.7	3	7.37	0	Cond.	1649.13	3	1.74	0.19
Sub.	27.51	7	6.34	0	Sub.	11694.3	7	5.3	0
Error	13.01	21			Error	6624.03	21		
Total	54.22	31			Total	19967.5	31		

Table D-2 ANOVA of the modulation frequency study – diotic stimulation

Amplitudes P1-N1					**Latencies P1-N1**				
Source	**SS**	**df**	**F**	**p**	**Source**	**SS**	**df**	**F**	**p**
Cond.	1.08	2	1.61	0.28	Cond.	162.33	2	0.38	0.7
Sub.	6.39	5	3.83	0.07	Sub.	683.75	5	0.64	0.68
Error	2	6			Error	1278.82	6		
Total	9.19	13			Total	2106.83	13		
Amplitudes N1-P2					**Latencies N1-P2**				
Source	**SS**	**df**	**F**	**p**	**Source**	**SS**	**df**	**F**	**p**
Cond.	3.02	2	1.17	0.36	Cond.	42.33	2	0.19	0.83
Sub.	26.96	5	4.19	0.04	Sub.	2464.86	5	4.31	0.03
Error	10.3	8			Error	914.69	8		
Total	38.83	15			Total	3529.03	15		
Amplitudes P2-N2					**Latencies P2-N2**				
Source	**SS**	**df**	**F**	**p**	**Source**	**SS**	**df**	**F**	**p**
Cond.	8.35	2	4.73	0.04	Cond.	303.33	2	0.92	0.44
Sub.	8.57	5	1.94	0.19	Sub.	4285.96	5	5.18	0.02
Error	7.07	8			Error	1322.67	8		
Total	21.44	15			Total	5884.32	15		

Table D-3 ANOVA of the rate study

Amplitudes N1-P2				
Source	**SS**	**df**	**F**	**p**
Cond.	31.16	2.00	21.11	0.00
Sub.	38.92	7.00	7.53	0.00
Error	10.34	14.00		
Total	80.42	23.00		
Amplitudes P2-N2				
Source	**SS**	**df**	**F**	**p**
Cond.	30.81	2.00	25.35	0.00
Sub.	24.86	7.00	5.85	0.00
Error	8.51	14.00		
Total	64.18	23.00		
Latencies N1-P2				
Source	**SS**	**df**	**F**	**p**
Cond.	41.97	2.00	0.11	0.90
Sub.	1041.67	7.00	0.76	0.63
Error	2739.66	14.00		
Total	3823.30	23.00		
Latencies P2-N2				
Source	**SS**	**df**	**F**	**p**
Cond.	225.37	2.00	0.34	0.72
Sub.	5764.48	7.00	2.46	0.07
Error	4678.44	14.00		
Total	10668.29	23.00		

Table D-4 ANOVA of the carrier frequency study

Amplitudes N1-P2				
Source	**SS**	**df**	**F**	**p**
Cond.	22.26	3.00	10.75	0.00
Sub.	69.54	6.00	16.79	0.00
Error	11.73	17.00		
Total	98.68	26.00		
Amplitudes P2-N2				
Source	**SS**	**df**	**F**	**p**
Cond.	27.50	3.00	21.45	0.00
Sub.	44.34	6.00	17.29	0.00
Error	7.26	17.00		
Total	71.91	26.00		
Latencies N1-P2				
Source	**SS**	**df**	**F**	**p**
Cond.	77.06	3.00	0.43	0.73
Sub.	1355.34	6.00	3.78	0.01
Error	1015.13	17.00		
Total	2520.11	26.00		
Latencies P2-N2				
Source	**SS**	**df**	**F**	**p**
Cond.	1148.90	3.00	1.03	0.40
Sub.	4042.35	6.00	1.82	0.15
Error	6296.04	17.00		
Total	11471.72	26.00		

Table D-5 ANOVA of the intensity study

Amplitudes N1-P2				
Source	**SS**	**df**	**F**	**p**
Cond.	10.43	3.00	5.89	0.01
Sub.	34.86	6.00	9.84	0.00
Error	7.68	13.00		
Total	46.29	22.00		
Amplitudes P2-N2				
Source	**SS**	**df**	**F**	**p**
Cond.	17.41	3.00	9.60	0.00
Sub.	25.55	6.00	7.04	0.00
Error	7.86	13.00		
Total	42.76	22.00		
Latencies N1-P2				
Source	**SS**	**df**	**F**	**p**
Cond.	293.13	3.00	0.35	0.79
Sub.	4090.58	6.00	2.43	0.08
Error	3645.94	13.00		
Total	8045.59	22.00		
Latencies P2-N2				
Source	**SS**	**df**	**F**	**p**
Cond.	3369.24	3.00	2.76	0.08
Sub.	7063.62	6.00	2.89	0.05
Error	5295.95	13.00		
Total	15213.32	22.00		