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UNIVERSITY OF MIAMI

ANALYSIS OF AUDITORY EVOKED RESPONSES ELICITED BY GAPS IN NOISE

By

Khalid Alhussaini

A DISSERTATION

Submitted to the Faculty
of the University of Miami
in partial fulfillment of the requirements for
the degree of Doctor of Philosophy

Coral Gables, Florida

May 2017

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ANALYSIS OF AUDITORY EVOKED RESPONSES ELICITED BY GAPS IN NOISE

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ALHUSSAINI, KHALID (Ph.D., Biomedical Engineering)
Analysis of Auditory Evoked Responses Elicited By Gaps in Noise (May 2017)

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Dissertation supervised by Professor Ozcan Ozdamar.
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Psychophysical detection of gaps embedded in ongoing sounds is commonly used to measure temporal resolution in hearing tests. Cortical auditory responses to such gaps in noise are investigated as electrophysiological assessment of temporal resolution. This study was conducted to investigate the characteristics of auditory evoked potentials (AEPs) to gaps in broadband noise. Transient responses such as Auditory Brainstem (ABR), Middle Latency (MLR) and Late latency (LLR) were recorded as well as 40Hz Auditory Steady-State Responses (ASSR) and Quasi ASSR generated by jittered 40Hz gaps. Gaps of short and long durations were presented at different rates to study the effect of rate and duration on AEPs. Also, the influence of gap onset/offset on the transient evoked responses was examined. AEPs were elicited at four rates 0.5, 1, 5, and 40Hz. 0.5Hz responses showed cortical waves while 1 Hz responses showed ABR, MLR and LLR components. 40 and 5 Hz responses were characterized by ABR and MLR components with no LLRs likely. For short gaps, results suggest that amplitudes of MLR, LLR and QASSR were affected by gap duration; as the duration decreases the amplitudes diminish. For long gaps, two distinct onset and offset responses were observed. Waveform changes as the gap shortens

from 300ms to 6ms suggest overlap of the onset and offset responses resulting in different AEP morphologies.

DEDICATION

To my son, Abdullah, who came to life during my graduate study journey and boosted my motivation

.

ACKNOWLEDGEMENTS

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CHAPTER 1: INTRODUCTION

Perceiving speech or music requires efficient brain ability to process small changes of sound in time. The ability of the brain to process tiny changes in sound over time is called auditory temporal resolution (Moore & Moore, 2003). One of the most used psychophysical tests to evaluate temporal resolution is gap in sound. Gap tests are basically sound stimulus (tone or noise) interrupted by short silence. The shortest gap duration perceived is assigned as the gap detection threshold. Typically, the minimum perceived gap duration is reported to be 2 to 3ms (Plomp, 1964). However, this gap detection threshold was reached after extensive training (Moore & Moore, 2003). Normal gap detection threshold recorded without training is about 4 to 5ms (Musiek et al., 2005).

Several factors such as auditory disorders and aging may contribute to poor temporal resolution. Poor temporal resolution may also be associated with speech perception complications (Gordon-Salant & Fitzgibbons, 1993). For example, aged individuals show poorer temporal resolution compared to young adults (Harris et al., 2012; Schneider et al., 1994). Other studies have linked poor temporal resolution to central auditory processing disorder and auditory neuropathy (Michalewski et al., 2005; Musiek et al., 2005). Additionally, some studies suggest that autistic individuals may have poor temporal resolution (Bhatara et al., 2013). Multiple sclerosis patients with normal pure tone hearing thresholds but having speech recognition difficulties, show poorer auditory temporal resolution when tested using gaps (Valadbeigi et al., 2014).

Currently, behavioral gap detection threshold tests are the most commonly used clinical tests to evaluate temporal resolution (Keith, 2000; Musiek et al., 2005). These tests are based on subjective feedback from the tested subjects or patients. In cases where behavioral testing is not feasible or extremely burdensome (e.g. pediatric, mentally ill), there exists a greater need for an objective method that evaluates the temporal resolution. Multiple studies have utilized auditory cortical responses to obtain gap detection thresholds (Harris et al., 2012; Michalewski et al., 2005; Palmer and Musiek, 2013; 2014; Pratt et al., 2005). These studies have found that gap in noise stimuli can evoke N1-P2 complex, and their thresholds match behavioral threshold. All these studies confirm that shorter gap durations evoke smaller N1-P2 complex; that is, shorter the gap, smaller the cortical response.

Electrophysiological responses to noise gaps not only could provide objective evaluation of temporal resolution, but they can also provide deeper insights to higher order skills in the central auditory system. However, most published studies were focused on recording late latency responses to gaps in noise (Atcherson et al., 2009; Harris et al., 2012; Lister et al., 2011; Michalewski et al., 2005; Palmer and Musiek, 2013; 2014; Pratt et al., 2005).

In addition to cortical responses, gaps in noise were also used to record auditory brainstem responses (Poth et al., 2001; Werner et al., 2001). Brainstem responses are more robust and can be easily obtained while the subjects are sleeping. They, however, do not provide assessment of higher cortical abilities.

Although some researchers studied temporal resolution by recording Auditory Evoked Potentials (AEPs), but the body of work involving temporal resolution evaluation is greatly focused on psychophysical tests. There is a great need to further investigate the use of gaps in AEPs in order to reach an optimal and objective method to evaluate auditory temporal processes. Our narrow knowledge of auditory responses to gaps in noise is mainly based on studying cortical responses, but there is still a need to explore other responses such as Auditory Brainstem Response (ABR), Middle Latency Response (MLR) and Auditory Steady-State response (ASSR) to further deepen the current understanding of temporal processing.

In this dissertation, we aimed to study auditory evoked responses elicited by gaps embedded in broadband noise. We recruited normal-hearing young adults to record LLRs, MLRs, ABRs and ASSRs to gaps. Gap duration effect on AEP components was the primary investigation target. Additionally, we explored the effect of rate (gap per second) on the morphology of auditory responses. Also, we introduced an objective method to obtain gap detection threshold. Finally, the morphology of gap offset and gap onset responses were investigated.

The following chapters include a literature review covering important aspects related to the dissertation goal. It discusses topics such as AEPs, auditory temporal processing, and gap studies highly relevant to the dissertation. The goal and specific aims are stated in the third chapter. The next chapter details the general methods followed by the experiments' design. The results are

presented for each experiment separately. And, in the discussion chapter, the results are discussed and compared with previous published studies.

CHAPTER 2: BACKGROUND

2.1 Human Auditory System

In order to understand how we perceive sound and how human brain is capable of distinguishing subtle characteristics in speech or music, it is essential to recognize the anatomical and physiological characteristics of the auditory system. Sound that hearing system can deal with is basically composed of vibrations travelling in air until it reaches the pinna. The hearing system which perceives sounds is classified into two parts; peripheral hearing system and central auditory system.

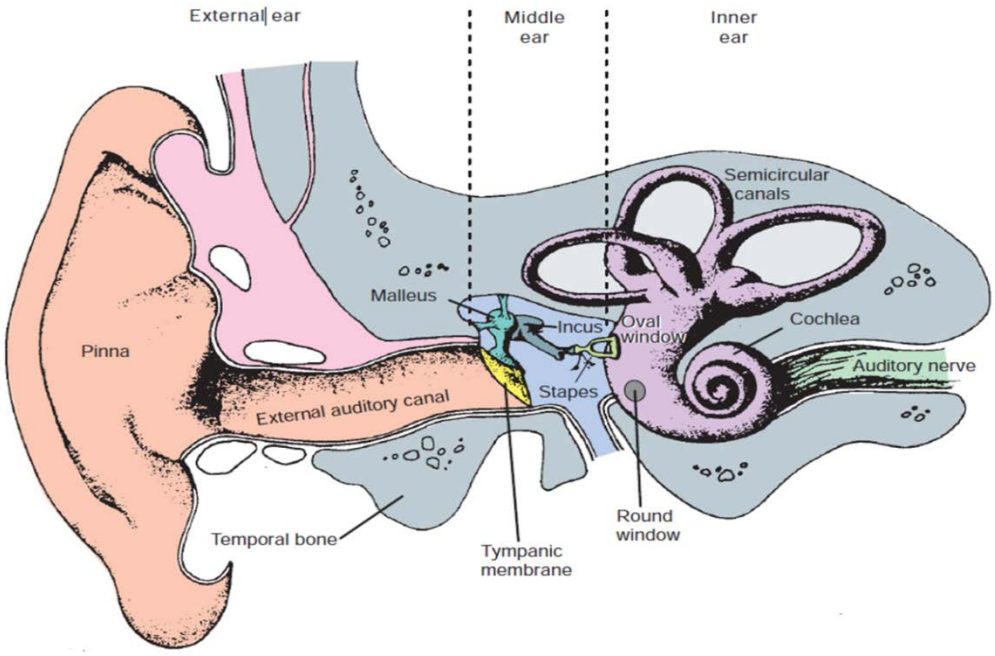

FIGURE 2.1 Illustration of the human auditory periphery. The external ear contains the pinna and external auditory canal. The middle ear, an air filled cavity, contains the tympanic membrane or eardrum, and the three middle ear ossicles: malleus, incus, and stapes). The inner ear contains the cochlea. From (Squire et al., 2012).

The peripheral auditory system is the first stage of hearing, and involves transduction of sound vibrations into neural impulses that are transmitted to the central auditory system for further processing. The peripheral hearing system as shown in Figure 2.1 is composed of the outer, middle and inner ear. The outer ear consists of the pinna, and the external ear canal, an air pathway between the exterior of the head and the middle ear.

The middle ear contains the tympanic membrane and three small bones, or ossicles, the malleus, the incus and the stapes, connected together to form a physical transduction chain between the external ear and the inner ear.

The inner ear contains components of both the auditory and vestibular systems. The cochlea is the primary neural transduction organ for the auditory system. Other non-auditory structures of semicircular canals, utricle and saccule comprise the vestibular system.

Stepwise, sound propagates in air until it reaches the pinna, which directs and focuses sound waves into ear canal. The pinna therefore plays a significant role in sound source localization. In the ear canal, sound waves transmitted to the tympanic membrane vibrates with respect to the acoustical characteristics of the sound wave.

On the other side of the eardrum is the middle ear. The main function of the middle ear is to act as an impedance matching pathway between the airborne acoustic energy coming from the outer ear into fluid of the cochlea (Squire et al., 2012, Ch. 26).

Acoustic energy arriving at the tympanic membrane in the external ear is transduced into mechanical energy in the middle ear by vibrations induced in the malleus, which is directly attached to the tympanic membrane. The mechanical vibration is then conducted through the remaining ossicles (the incus and stapes). (Squire et al., 2012, Ch. 26). Additionally, in the middle ear contains two muscles connected to the bony structures which are tensor tympani muscle and stapedius muscle which increase the effective damping on the ossicles to reduce transmitted energy, and thereby reduce damage to the cochlea by loud sounds.

The following stage includes transduction mechanical energy from the middle ear to neural activity in the cochlea. The mechanical vibration of the stapes at the oval window results in a fluid wave the uncompressible fluids in the cochlea. The process of how the movements of the fluid inside the cochlea produce electrical impulses is well explained in the literature (see Bear et al., 2006, Chapter 11 or Squire et al., 2012, Chapter 26).

Neural impulses generated by the cochlea are then transmitted through the eighth cranial nerve, or auditory nerve, to the central hearing system. Figure 2.2 illustrates the anatomical pathway in the central hearing system; as shown the path is passing through the brain stem and midbrain, ending at the auditory cortex.

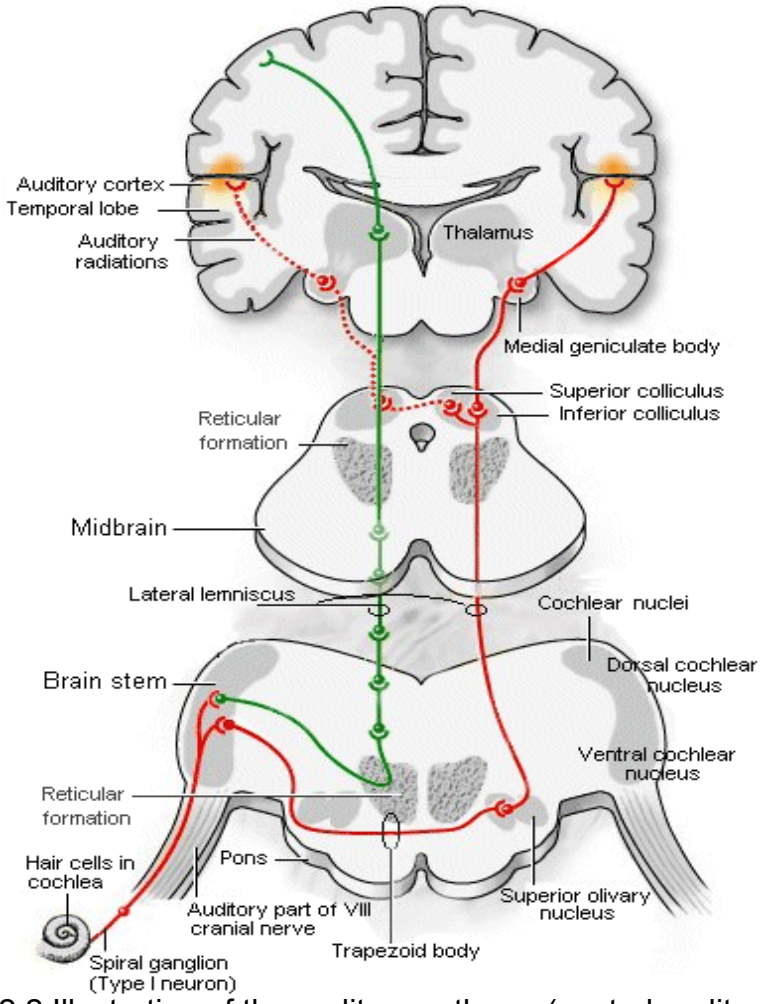

FIGURE 2.2 Illustration of the auditory pathway (central auditory system).Source http://firstyears.org/anatomy/ear.htm

2.2 Auditory Evoked Potentials (AEPs)

The integrity and functionality of the auditory system can be assessed by many different approaches. One of the most basic assessments of hearing in humans is a behavioral test which requires the cooperation of the subject to report if they heard the sound or not. Short duration sounds are played at various intensities and frequencies, and the subject's threshold's responses are recorded. The resulting audiogram is a measure of hearing acuity across various

frequencies. However, in some testing scenarios (e.g. newborns); patient feedback is not possible. In such cases, objective hearing assessments are used. A few examples of objective measures include otoacoustic emission (OAEs), and various form of evoked potentials (EPs). The Auditory brainstem response (ABR) is an evoked potential that is a direct measure of early auditory neural conduction integrity. This section will be focused mainly on auditory evoked responses.

Auditory evoked responses represent small changes in the spontaneous electroencephalogram (EEG) in response to auditory stimuli. These responses are obligatory and are time (and phase) locked relative to the auditory stimulus. Since AEPs are time locked responses, they can be isolated from unwanted EEG activity by employing numerous averaging techniques. In the conventional averaging technique, an auditory stimulus (click, tone burst, speech...etc.) is presented repeatedly to the ear. Adequate time intervals between each stimulus is maintained to ensure that the AEP evoked in response to one stimulus is completed prior to presenting subsequent stimuli to prevent overlapping of multiple AEPs. Signal averaging is performed by synchronously adding all responses which causes the random EEG background activity to partially cancel out, and the time locked AEP is preserved. The transient Auditory Evoked Potentials fall into three main classes: the Auditory Brainstem Responses (ABRs), Middle Latency Responses (MLRs), and Late Latency Responses (LLR). The ABR, MLR and LLR are common viewed as time domain signals. Auditory Steady-State Responses (ASSRs) result when stimuli are presented rapidly and

responses become overlapped. ASSRs can be evaluated in the frequency domain by analyzing the phase and the magnitude.

2.2.1 Auditory Brainstem Responses

Auditory brainstem responses are set of consecutive distinct waves that appear in the first 9ms following stimulus onset. In normal hearing subjects, ABRs are comprised of seven vertex-positive wave components, labelled with Roman numerals from wave I to wave VII (Jewett & Williston, 1971). Peak V is the most prominent peak due to its high amplitude relative to the rest of the ABRs peaks. Moreover, The ABRs are considered to be fully exogenous responses (Picton, 2011, Ch.8).

The neural generators of each peak of ABR are fairly well known; Figure 2.3 summarizes the generators in central auditory system (Waxman, 2010). The distal portion of the auditory nerve (8th cranial nerve) is believed to be the source of peak I in the ABR (Møller and Jannetta, 1981). Peak II is believed to be generated from the proximal portion of the auditory nerve (Møller and Jannetta, 1981). Peak III is believed to be generated as a result of activation in the superior olivary complex (SOC) (Waxman, 2010). Cochlear nucleus and nucleus of lateral lemniscus are believed to be the source of the peak IV (Waxman, 2010).

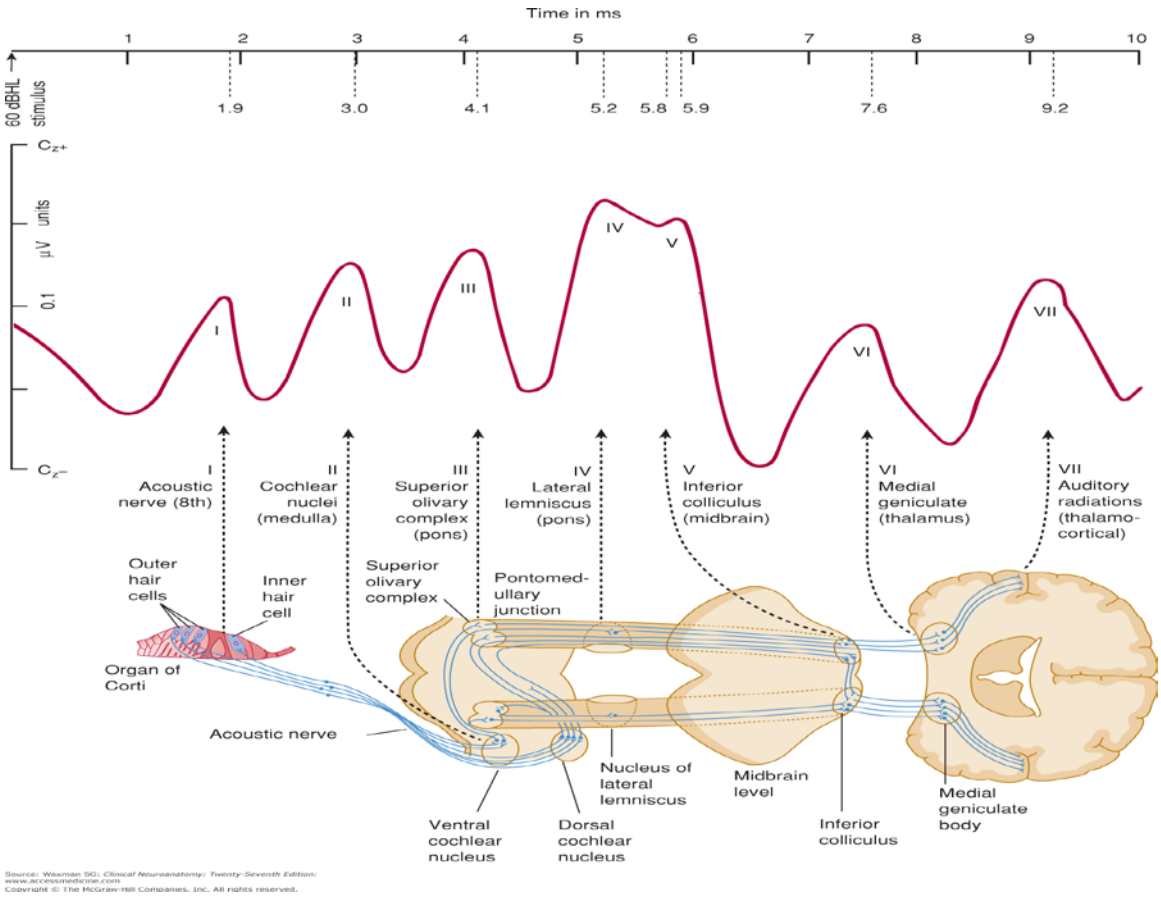

FIGURE 2.3 Illustration of the auditory brainstem responses generators in central auditory system from (Waxman, 2010)

Peak V, typically the most prominent peak, is believed to be neural activity in the lateral lemniscus within the region of the SOC to inferior colliculus (IC) (Picton, 2011, Ch. 8). Peak five is considered to be a stable component in ABR because of its insensitivity to high stimulation rates (Picton et al., 1977).

The ABR is the most widely used electrophysiological tool to assess the auditory system. The amplitude and latencies of the seven peaks of ABR; especially peak five, can be utilized to assess a subject's hearing level, detect lesions in the auditory pathway, or for intraoperative monitoring (Burkard et al., 2007, Ch.12).

The ABR is also known for its insensitivity to sedation or sleep which make it a suitable tool to evaluate hearing levels in newborns or uncooperative patients (Picton et al., 1977). Hearing thresholds can be evaluated using ABRs evoked by various stimulus frequencies and intensities as shown in Figure 2.4. As shown in the figure, as stimulus intensity decreases, peak latencies become prolonged and amplitudes diminish until peak five can no longer be identified. The hearing threshold level is determined from the lowest intensity where peak V can be classified.

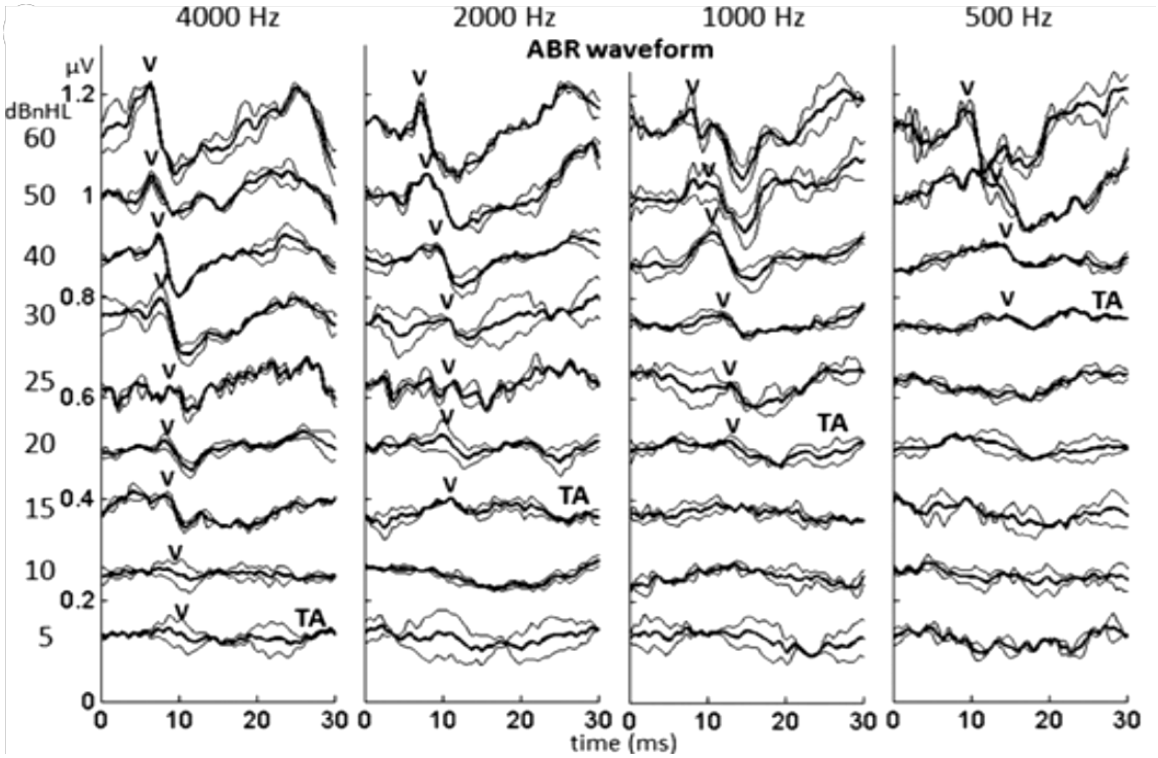

Figure 2.4 ABRs evoked by four carrier frequencies (500, 1000, 2000 and 4000 Hz), in each condition the intensity decreases until the threshold is assigned (Lachowska et al., 2012).

2.2.2 Middle Latency Responses

The second set of transient auditory evoked potentials is called Middle Latency Responses (MLRs). Peaks of MLRs start just after ABRs and last up to roughly 50ms (Picton et al., 1974). MLRs peaks are conventionally named according to its positivity (P) and negativity (N). As illustrated in Figure 2.5, the five peaks of MLRs are labelled respectively as (N_o, P_o, N_a, P_a, and N_b) (Picton et al., 1974). Components of MLRs may differ in morphology and amplitudes depending on various factors. These factors include age, wakefulness, recording parameters (Burkard et al., 2007, Ch. 22) and stimulation rate (Holt & Ozdamar, 2015). Subject age also effects latency of MLRs, when recorded from infants; latencies of MLR peaks are longer than adults (Picton, 2011, Ch. 9). Moreover, during sleep, wave components of MLRs can still be identified but with smaller amplitudes and longer latencies (Picton, 2011, Ch. 9). However, among the components of MLRs, Pa is considered the most consistent peak (Burkard et al., 2007, Ch.22; Picton, 2011, Ch9).

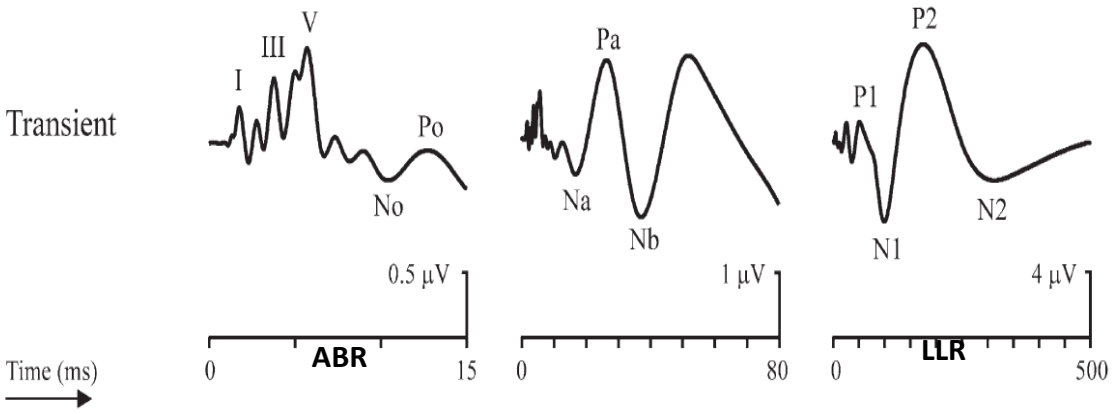

FIGURE 2.5 ABR, MLR and LLR evoked by 70 dB nHL clicks presented at a rate of 1 per sec. Modified from (Picton, 2013)

Unlike ABRs, the neural generators for MLR peaks are less well understood in terms of the auditory pathways. However, it is believed that a combination of multiple generators contribute to MLR peaks (Ozdamar & Kraus, 1983; Picton, 2011, Ch9).

The first negative component, N_o, is believed to be originated in the brainstem while the second negative component N_a is believed to be generated from midbrain, thalamus or thalamocortical radiations (Burkard et al., 2007, Ch.22). Pa, which has latency around 25m is considered as the most prominent peak in the MLR, is thought to be originated from the primary auditory cortex with contribution from the reticular formation and medial geniculate body (Burkard et al., 2007, Ch.22). Pb (or sometimes called P1) appears 25ms after Pa and considered the second prominent peak in MLR, but is less constant than Pa (Burkard et al., 2007, Ch.22)

There have been several attempts to use MLR as diagnostic tool for assessing auditory functions, sleep stages or neural complications. The use of MLR to diagnose patients with cortical deafness or cortical lesions has been investigated (Burkard et al., 2007, Ch.22; Kraus et al., 1982; Ozdamar et al., 1982). Furthermore, MLRs has been considered as potential tool which can be utilized to monitor the depth of anesthesia (Picton, 2011, Ch9; Thornton & Newton, 1989). The MLRs has also been demonstrated to exhibit traceable changes in amplitude and latency across sleep stages (Picton, 2011, Ch9).

2.2.3 Late Latency Responses

Late (or Long) Latency Responses (LLRs) are named according to their relative latency after earlier auditory evoked responses. LLRs are waveform components seen between 50ms and 250ms. The LLRs contains four peaks named conventionally as P1, N1, P2 and N2, respectively (Picton et al., 1974). LLRs components are characterized by their large amplitude compared with ABRs and MLRs as shown in Figure 2.5. P1, which has a latency of about 50ms-60ms after stimulus onset, may also be considered part of the MLR component Pb (Ozdamar & Kraus, 1983; Picton, 2011, Ch11). P1, however, is small in amplitude and not observed well when restrictive filtering is used and as a result its analysis is omitted in most articles. The prominent peaks N1 and P2 are commonly grouped together and named as N1-P2 complex. In normal human subjects, N2 appear 250ms after stimulus onset and its amplitude is enhanced noticeably in sleep (Picton, 2011, Ch11).

Long latency responses are believed to be generated from the auditory cortices with contribution from other cortices (Picton, 2013). In particular, the P1 component is known to be generated from the primary auditory cortex with contribution from other regions, including the hippocampus, planum temporal, and lateral temporal cortex (Burkard et al., 2007, Ch.23). Generators of N1 have also been identified in the primary and the secondary auditory cortex (Burkard et al., 2007, Ch.23). As result of contribution of multiple cortices in LLRs generation, LLRs are considered mostly as endogenous responses (Picton, 2011, Ch11). LLRs have been challenging to study due to the variability caused by multiple

factors. Some of these factors are related to the subject state; maturation, age, gender, state of arousal, and attentiveness (Burkard et al., 2007, Ch.23).

Typically, the ABR, MLR and LLR are recorded and studied independently. However, the possibility of recording components from all epochs of the AEP simultaneously has been demonstrated, including the ABR (peak V), MLR and LLR simultaneously. Figure 2.6 shows AEP recorded in 500ms recording window using chirp stimulus (Holt and Ozdamar, 2015).

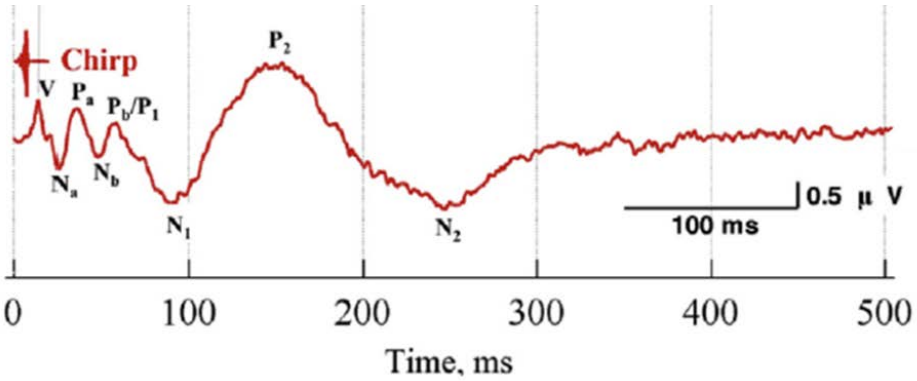

FIGURE 2.6 Waves V, Na, Pa, Nb, Pb/P1, N1, P2, and N2 recorded simultaneously. 250 sweeps acquired at 0.98/s repetition rate. Modified from (Holt and Ozdamar, 2015).

2.2.4 Auditory Steady-State Responses

Auditory Steady-State Responses (ASSRs) were first reported by Galambos et al. (1981). ASSRs are a periodic response characterized by uniform phase and amplitude. In general, ASSR has a phase that follows the rate of stimulation. Additionally, to generate ASSR, the rate of stimulation must be high enough to cause overlapping of transient responses. Figure 2.7 illustrates how the response changes with stimulation rate for a tone burst rate from 3.3Hz to 40Hz. Unlike transient auditory evoked responses which are commonly

described with respect to their amplitudes and latencies, ASSR is primarily evaluated in the frequency domain and described by magnitude and phase.

Additionally, ASSR can be represented using a unit circle to plot the magnitude of the signal versus the phase (Picton et al., 2003a). 40 Hz ASSR is considered the most robust response because of its prominent peaks and ease of detection. However, the 40 Hz ASSR responses are significantly affected by sleep (Picton et al., 2003b). The 80 Hz ASSR is less affected by sleep (Burkard et al., 2007, Ch.23).

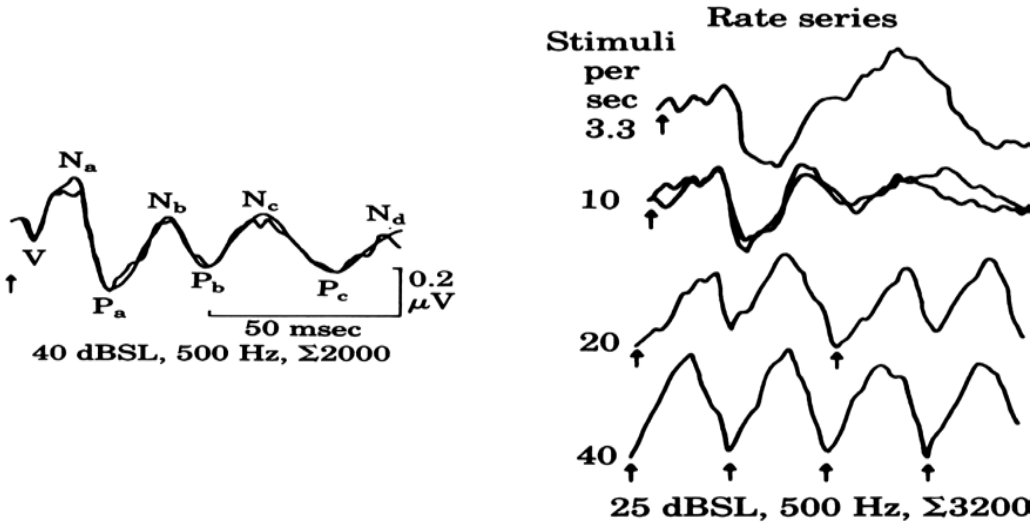

FIGURE 2.7 Response to 500 Hz tone burst, different rate series shown between 3.3 Hz up to 40Hz. Modified from (Galambos et al., 1981).

In audiometry, the 40 Hz ASSR is commonly used to provide an accurate and relatively fast assessment of hearing level for waking adults. Higher stimulation rates including the 80 Hz ASSR have been also investigated to estimate the behavioral hearing threshold for adults, older children and newborns (Dimitrijevic et al., 2002; Picton et al., 1998; Picton et al., 2005). In general, 80Hz ASSR was presented as a more useful objective tool to assess hearing level. ,

The ASSR is more suitable to assess the hearing of newborns only when utilizing faster rates (greater than 40Hz) (Picton et al., 2003a; Rance and Rickards, 2002; Rance, 2005).

2.3 Acquiring Auditory Evoked Potentials

Event-Related Potentials are responses that can occur as a result of specific sensory stimulation, and appear superimposed on background EEG activity. In this section, methods for recording EEG signals are described, as well as methods for extracting auditory evoked potentials from the raw EEG. First, the conventional acoustic stimuli used to evoke auditory responses are detailed as well as more complex acoustic stimuli. Then, the ordinary signal processing techniques in addition to other techniques such as deconvolution are described.

2.3.1 Stimulation

Several factors that may have a significant impact on the presence, detectability and morphology of conventional AEP components, some factors are related to the subject being recorded (gender, maturation, level of attention, etc.). Additionally, characteristics of the stimulus used to evoke AEPs have a clear influence on the features of the recorded AEPs. In the current section, only the properties of different acoustic stimuli used to elicit AEPs are discussed, such as stimulus intensity, duration, and stimulation rate.

Acoustic clicks are one of the most common acoustic stimuli used to evoke AEPs. Technically, clicks are generated by passing a rectangular pulse of voltage (100μV width) through a transducer (Picton, 2011, Ch.5). Practically, click stimuli can be considered as broadband, but are subject to two limitations: the

pulse width and the bandwidth of the transducer (Burkard et al., 2007, Ch.3). Panel A of Figure 2.8 illustrates the physical characteristics and spectral contents of a click before it is passed through a transducer (e.g. ER-3A, Etymotic Research, Elk Grove Village, IL) and after. Tone bursts and frequency modulated chirps are other type of commonly used acoustic stimuli. For both objective and subjective audiometric testing, tone bursts are often the best option (Burkard et al., 2007, Ch.21). Furthermore, chirps can be utilized to evoke AEPs which has its advantages disadvantages over other stimuli, for more details see (Picton, 2011, Ch.5).

Speech syllabi, white noise and gaps in noise or tones are some other types of more complex stimuli used in auditory research. Figure 2.8 illustrates some of these stimuli presented in the time and frequency domains. The selection of stimulus depends on its features and there impacts on the resulted AEPs. An example of speech stimulus can be a vowel constructed and digitized then introduced as acoustic stimulus. One of the parameters which the AEPs may depend on is the frequency contents of such stimuli (Picton, 2011, Ch.5). Gaps in noise stimuli are the main focus of the current work and it will be covered in detail later.

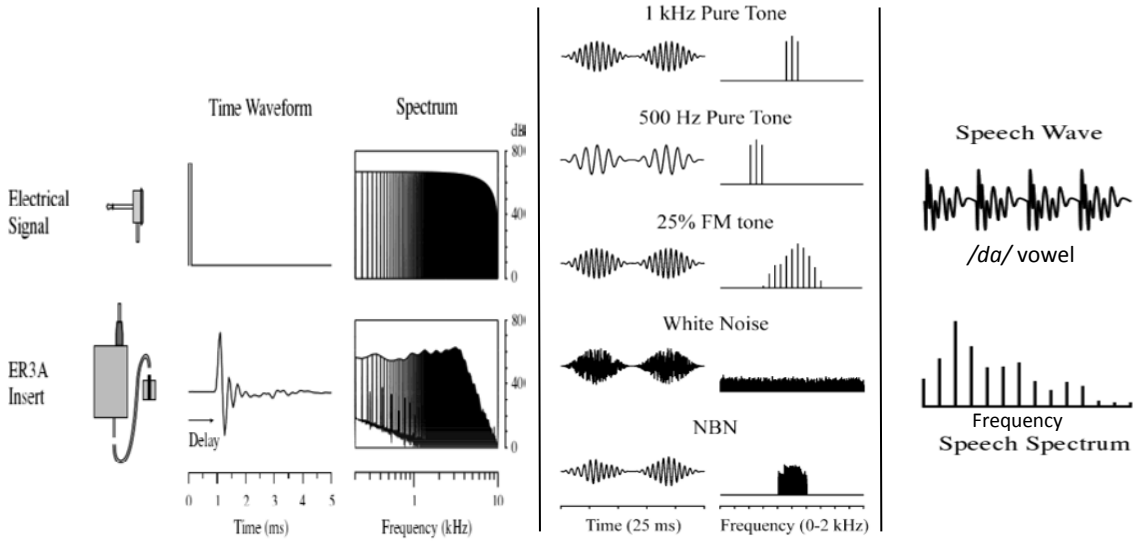

FIGURE 2.8 left top, 100μs click pulse with its frequency spectrum. Left bottom, acoustic click after passing through ER3A transducer. Middle, multiple acoustic stimuli (pure tones, frequency modulated tone (FM tone), white noise, and narrow band noise (NBN). Right, speech stimulus with its frequency spectrum. Modified from (Picton, 2011)

Stimulus intensity has a direct relationship with AEP amplitude. In general, intensity has been utilized mainly in objective and subjective audiometry as the amplitude of AEPs reduces with lower intensities. AEPs are also sensitive to the stimulus presentation rate. As explained earlier, transient responses are evoked by lower stimulation rates (<3Hz), while steady state response needs higher rates to cause overlapping of transient responses. Several rate studies have shown an effect on AEPs amplitude and latency as function of rate (Holt & Ozdamar, 2015). A recent rate study conducted by Holt & and Ozdamar (2015) showed that AEP peak latencies remain stable across different stimulation rates (0.3-40Hz), except the P2 component. On the other hand, components amplitude of ABR, MLR, and LLR were affected by the rate of stimulation.

2.3.2 Averaging and Signal Processing

Auditory evoked potentials are analyzed typically in one of the two following views; transient responses in time domain, while ASSRs are typically analyzed in the frequency domain. However, the traditional method to obtain both responses from EEG is the same. Since all EPs are time-locked potentials, they can be attained using traditional synchronous averaging. Averaging is the most common technique used to extract relatively small AEP responses (~0.1μV) embedded in random background EEG signal (~100μV). The averaging procedure is based on the summation of EEG slices called “sweeps,” which are time-locked to the stimulus onset. Since the responses to the stimulus within each sweep is time-locked, while all other EEG activity is random. The number of sweeps acquired and averaged dictates the potential signal-to-noise (SNR) for the AEP. Enhancement of SNR as function of sweep number is assumed to be a factor of the square root of the number of sweeps (Burkard et al., 2007, Ch.4). Figure 2.9 illustrates how increasing the number of sweeps improves the quality of the signal of interest.

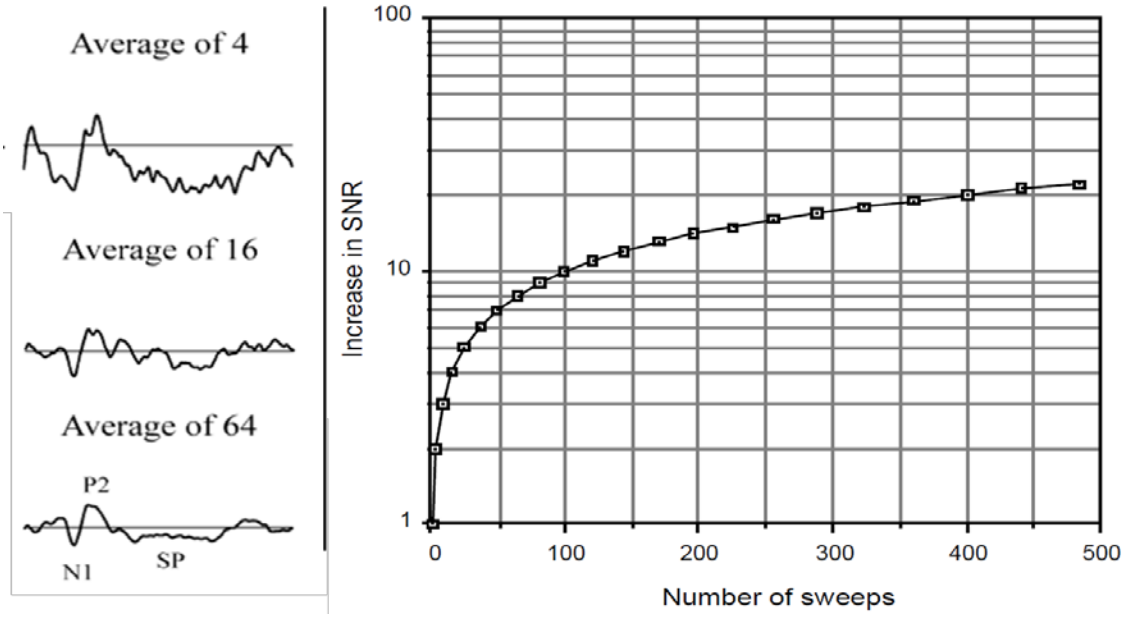

FIGURE 2.9 Left panel illustrates how the number of sweeps plays a role on LLR morphology as the number increases, modified from (Picton, 2011, Ch2). Right panel shows SNR as function of the square root of the number of sweeps, from (Tompkins, 1993).

2.3.3 Continuous Loop Averaging Deconvolution (CLAD)

Generally, recording transient evoked responses using conventional averaging requires the stimulation rate to be low enough to prevent overlapping. In other words, the time interval between stimuli should allow the completion of the transient response before the next stimulus is presented. For example, recording ABRs which appear in the first 12-15ms, the stimulation rate generally should be below 67-83Hz to prevent overlapping (Ozdamar et al., 2007). However, when overlapping occurs as a result of high stimulation rate, the temporal characteristics of the responses become obscured but it can be recognized as ASSRs as shown in Figure 2.10.

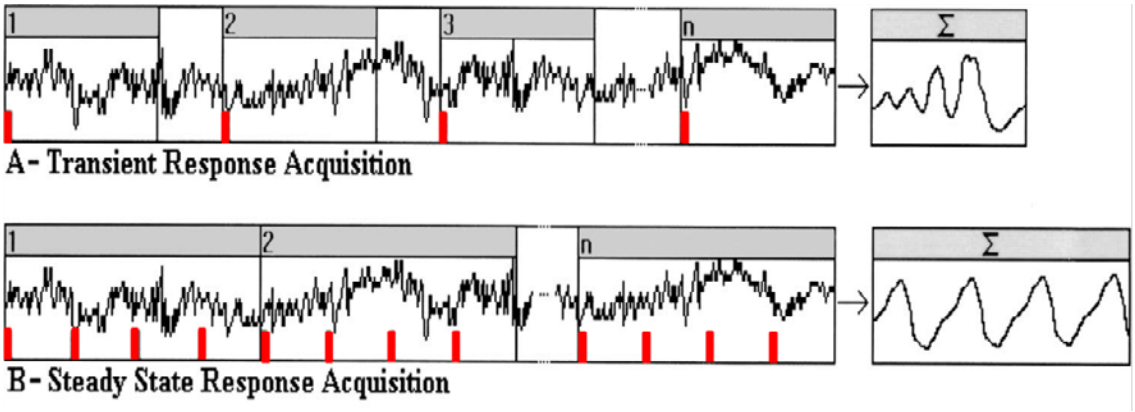

FIGURE 2.10 A) Transient responses using conventional averaging method. B) Steady state responses using conventional averaging method. Modified from (Delgado &Ozdamar, 2004)

As mentioned earlier, recording transient responses with good SNR requires sufficient number of sweeps and limited stimulation rate based on the length of desired responses. The response duration constraint in conventional averaging limits the ability to study high rate effect on the auditory system. Additionally, for high stimulation rates, the resulting ASSR can only be analyzed in terms of phase and magnitude. To overcome these constraints Delgado & Ozdamar (2004) proposed a novel acquisition and processing technique called Continuous Loop Averaging Deconvolution (CLAD). The CLAD method provides a way to deconvolve the overlapped responses evoked by high stimulation rates. One of the key points in the CLAD method is the unequal (or non-isochronic) inter-stimulus-interval within the stimulus sequence. In other words, responses to individual stimuli can be obtained only if the deconvolution algorithm is applied to overlapped response evoked by the CLAD sequence (Delgado & Ozdamar, 2004)

The process of deconvolution is explained mathematically in the time domain in Delgado & Ozdamar (2004), by using matrices. It requires obtaining data using a continuous loop buffer **v[t]** which includes the summation of all separate responses. By assuming that the response to each stimulus, **a[t],** is independent, the vector of convoluted responses, **v[t],** is related to **a[t]** with the following equation: **v[t] = M a[t]**; where **M** is the multidiagonal matrix with a sequence of ones and zeros based on the stimulus sequence. The estimated response to an individual stimulus (or the estimated transient response) can be obtained by solving for **a[t]** as follows: $\mathbf{a[t] = M^{-1} v[t].}$

Although the deconvolution method provides an estimate of the transient response to high-rate stimulation, it has some caveats. Improperly designed sequences may result in unwanted noise, and the time taken to apply the deconvolution method is relatively long. To minimize these limitations, Ozdamar & Bohórquez (2006) proposed an alternative method of the deconvolution procedure in the frequency domain. The deconvolution method in frequency domain is faster as a result of using the fast Fourier transform (FFT) algorithm. Additionally, use of the frequency domain allows for a method of estimating and limiting the undesired noise characteristics of CLAD sequences. A brief description on how the deconvolution method is performed in both the frequency domain is illustrated in Figure 2.11 (Ozdamar & Bohórquez, 2006).

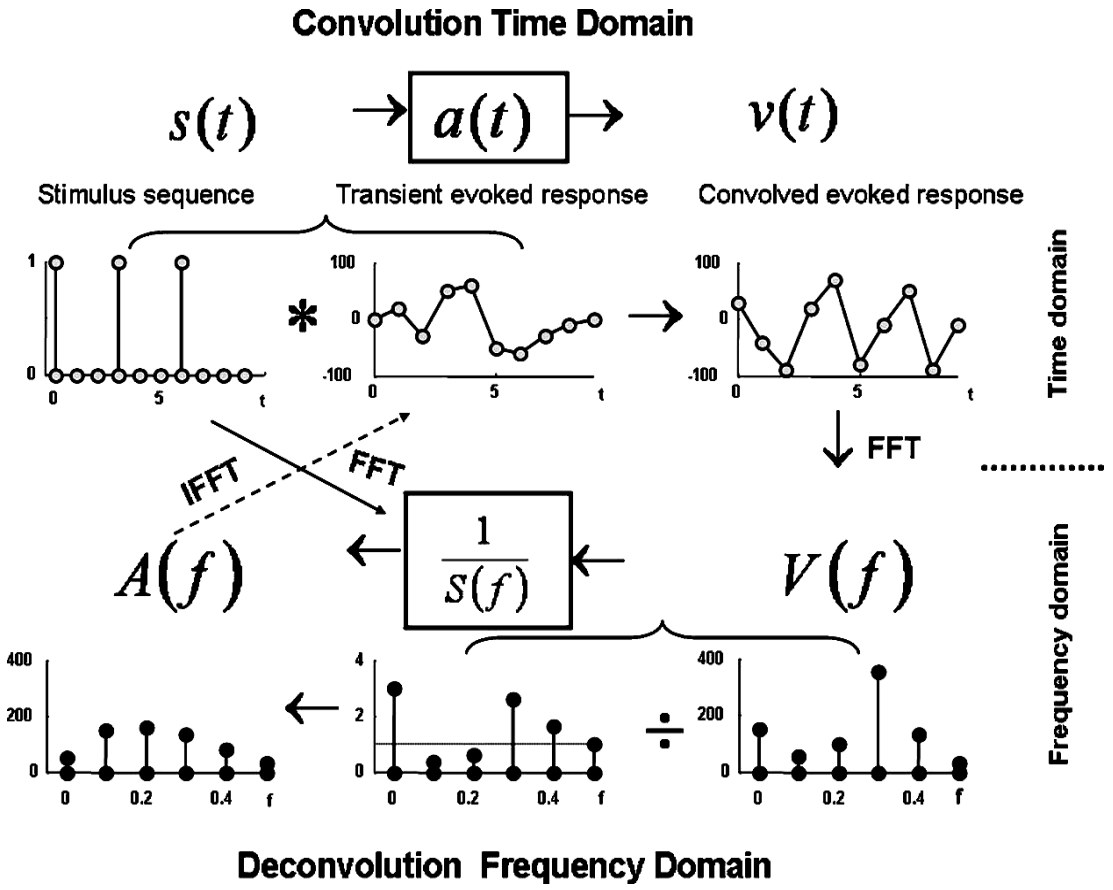

FIGURE 2.11 Convolution of the elementary responses to a stimulus sequence in the time domain produces a convolved response (top) and the deconvolution of the convolved response into the elementary response in the frequency domain (bottom). From (Ozdamar & Bohórquez, 2006)

2.4 Auditory Temporal Processing

The auditory system in normal subjects is capable of detecting subtle temporal changes in sound. The ability to perceive tiny changes in sound over time facilitates speech understanding (Moore and Moore, 2003, Ch5). Therefore, it is essential to understand the concept of auditory temporal processing and its disorders. Auditory temporal processing is defined by Musiek et al. (2005) as “the perception of the temporal characteristics of a sound or the alteration of durational characteristics within a restricted or defined time interval”. Auditory temporal processing can be seen from two aspects in time; temporal integration and temporal acuity (Eggermont, 2015).

Temporal integration is the ability of the auditory system to sum up (integrate) sound cues over time to improve the perception of sound (Moore and Moore, 2003, Ch. 5). Temporal integration process can be represented when long duration sounds are perceived before short duration sounds; this mechanism is called time-intensity trade (Moore and Moore, 2003, Ch6). On the other hand, temporal acuity (resolution) is defined as “the ability to detect changes in stimuli over time, for example, to detect a brief gap or detect that sound is modulated in some way” (Moore and Moore, 2003).

Speech as an acoustic signal contains both temporal cues and frequency content which are analyzed by the auditory system. In order to perceive the speech, auditory system should be able to detect these small cues. Therefore, some speech recognition difficulties result from degraded temporal processing sensitivity, which is often experienced by the elderly people in difficult listening

situations. For example, speech recognition may become degraded when background noise levels increase. Temporal processes have been investigated to explore the relationship between speech recognition and poor auditory temporal processing components (Gordon-Salant and Fitzgibbons, 1993; Rosen, 1992).

Assessment of auditory temporal processing can be investigated using multiple testing paradigms. For example, in order to assess temporal resolution, one early study focused on temporal ordering by introducing two tone bursts with different frequency and same time duration, and asked subjects to report which of the pair of frequency tone burst started first (Hirsh, 1959). In a later study, (Leshowitz, 1971) measured the shortest detectable temporal gap between a pair of click stimuli.

Another method of measuring temporal discrimination is by testing listener's ability to distinguish between stimuli that have slightly different frequency spectra (Moore, 1995, Ch.6). Furthermore, an alternative discrimination task which has been used to evaluate temporal acuity is amplitude modulation detection. Listeners' sensitivity to distinguish between modulated noise signals provides an estimation of temporal acuity; such testing paradigms can be performed by modulating the amplitude of either a broadband or narrowband noise signal (Moore, 1995, Ch.6).

In general, auditory processing deficits are usually accompanied or caused by neurological complications such as auditory neuropathy or multiple sclerosis (Eggermont, 2015). Additionally, maturation and aging have been

shown to be significant factors that influence temporal auditory processing. Even in the absence of significant hearing loss, aging has been reported as a cause for poor temporal auditory processing abilities (Eggermont, 2015). Moreover, conditions like dyslexia or specific language impairment (SLI) are presumed to be caused by auditory processing deficits (Eggermont, 2015; Tallal, 1980).

According to the American speech-language-hearing association (ASHA), Auditory Processing Disorder (APD) is defined as “a deficit in the processing of information that is specific to the auditory modality” (Jerger & Musiek, 2000). The ASHA working group has suggested multiple screening tests to aid in diagnosing school-age children with APD. The suggested test battery includes both behavioral (pure-tone audiometry, word recognition, dichotic task, duration pattern sequence test, and temporal gap detection) and objective (immitance audiometry, otoacoustic emission, ABR, and MLR) measures (Jerger & Musiek, 2000).

Finally, the detection of short gaps in an ongoing sound has been used extensively as a way to assess temporal resolution. However, gaps in an ongoing sound is the main focus of the current work, thus it will be covered in depth in the following sections.

2.4.1 Gaps in Sound Measures

Another method that has been used to evaluate auditory temporal processing resolution is the introduction of short duration gaps in an otherwise ongoing sound. Short gaps have embedded in various types of sound, such as pure-tones, broadband, and narrowband noise in order to evaluate how the

peripheral and central auditory system is able to detect subtle changes in sound. This section reviews current literature on gaps in sound with an emphasis on gap in noise from different aspects. First, the behavioral gap tests used to evaluate temporal resolution is discussed. Then, several studies utilizing evoked potentials to study gaps in noise to are discussed. It is important to show how stimulus design may have a significant impact on both behavioral and objective outcomes. Finally, we will illustrate how gaps in noise paradigms have been used to study the performance of the auditory system in different groups; including aging populations, individuals with neurological disorders and others.

2.4.2 Psychophysical Measures

One method of psychophysically evaluating temporal resolution is to insert a short gap in sound, and then asking the subject if he or she was able to detect the gap. An early gap detection paradigm was introduced by Plomp (1964); composed of two pulses of white noise separated by a short gap. He found that normal hearing subjects can detect gaps in otherwise continuous noise as short as 2-3ms. However, 2-3ms gap thresholds required extensive training, and gap detection thresholds below 7ms are considered to be normal (Musiek et al., 2005; Phillips and Smith, 2004). The versatility of gap thresholds could be explained by the subject factors (e.g. training, age) or the design specifications of the acoustic stimulus (Moore, 2003; Musiek et al., 2005; Phillips and Smith, 2004).

Several commercially available tests have been developed for auditory temporal resolution assessment; some of these tests are Gap in Noise (GIN©), Random Gap Detection Threshold (RGDT) and Auditory Fusion Test-Revised (AFT-R) (Keith, 2000; McCroskey and Keith, 1996; Musiek et al., 2005; Yalçınkaya et al., 2009). In AFT-R, subjects listened to two tones separated by a gap, then asked if they perceived one or two tones (Ahmmed et al., 2006). RGDT is also based on using gaps in tones of multiple carrier frequencies (500, 1000, 2000 and 4000 Hz) (Yalçınkaya et al., 2009). On the other hand, GIN is based on inserting gaps in noise instead of tones.

The GIN test was introduced by Musiek et al. (2005), to be used in clinical practice to evaluate temporal resolution in normal hearing subjects, as well as patients with central auditory nervous system impairment. The design of the GIN test is illustrated in Figure 2.12, Up to three separate short-duration gaps are embedded randomly in a 6 second segment of white noise. During the course of testing, gaps ranging from 2ms up to 20ms are presented in a random fashion repeatedly. The total time required to administer GIN test is around 17 minutes which make it feasible to be used in the clinics (Musiek et al., 2005).

Musiek et al. (2005) showed that the mean gap detection threshold of normal-hearing subjects is 4.9ms while the mean threshold of subjects with confirmed neurological hearing impairment of the central auditory system is 8.5ms. Elevation of the gap detection threshold in subject with central auditory system lesions makes GIN test sensitive to such neurological complications (Musiek et al., 2005; Rabelo et al., 2015). Additionally, the GIN test has been

demonstrated as a viable tool to evaluate temporal resolution in children 7 years and older (Shinn et al., 2009). Furthermore, using psychophysical gap detection tests, Bhatara et al. (2013) found that autistic subjects have higher gap detection thresholds when compared with normal subjects. This study evaluated auditory temporal resolution by using short gaps embedded in both tones and noise. Additionally, they found that individuals with ASD who had elevated gap detection threshold also have higher speech in noise test score (Bhatara et al., 2013).

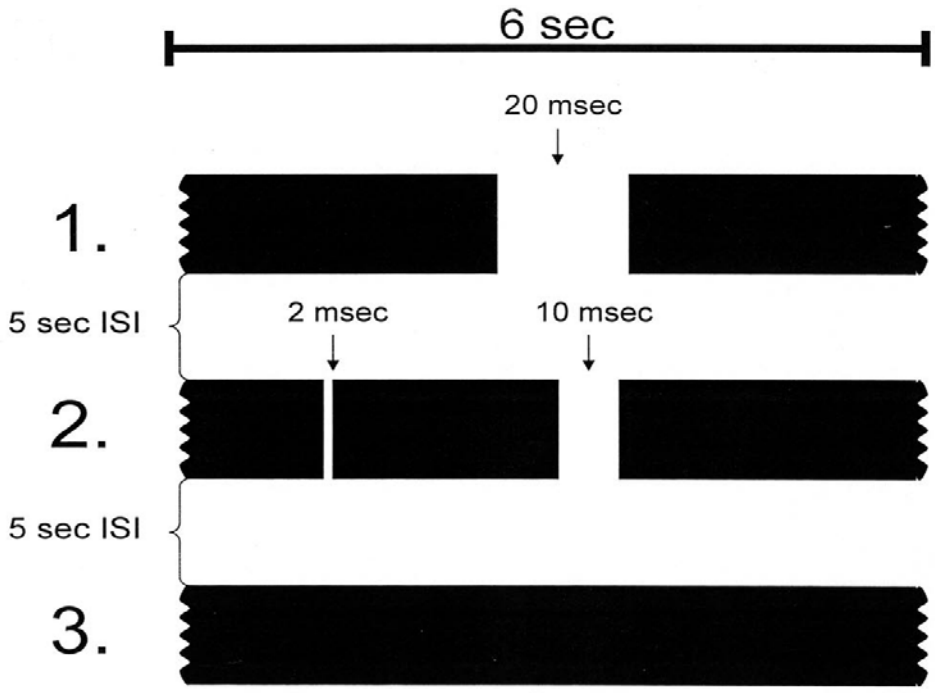

FIGURE 2.12 Samples of three GIN items demonstrating the duration of the stimuli, Inter-Stimulus Intervals (ISI), and varying durations. Modified from (Musiek et al., 2005)

2.5 Gap Electrophysiological Measures

The previous sections discussed some of the psychophysical gap detection tests and their ability to measure of temporal resolution based on the gap detection thresholds. However, some subjects populations cannot be tested psychophysically using such testing paradigms. Infants and young children are one example of such populations where they cannot reliably cooperate for behavioral testing. To address this issue, several studies have investigated AEPs evoked by gaps in sound as an objective assessment rather than behavioral assessment. Additionally, AEPs evoked by complex acoustic stimuli such gaps in noise may provide an insight of how AEPs morphology and latency differ from AEPs evoked by conventional audiometric stimuli (e.g. clicks). Comparison between behavioral gap thresholds and AEPs may explain the elevation of the gap detection thresholds in some populations like elderly subjects.

This section reviews some of the studies which have used gaps in noise or tones to evoke AEPs. The majority of studies using gaps in noise found in the literature were focused mainly on LLRs (Atcherson et al., 2009; Harris et al., 2012; Lister et al., 2007; Lister et al., 2011; Michalewski et al., 2005; Pratt et al., 2005). There has been less focus on ABRs recorded in responses to silent gaps in noise (Poth et al., 2001; Werner et al., 2001), and the author knows of no currently published work on MLRs or ASSRs to gaps in noise other than that described in the following chapters (Alhussaini et al., 2015).

However, some researchers have studied mismatch negativity (MMN) elicited by gaps embedded in tone burst to evaluate the temporal resolution (Bertoli et al., 2002; 2001). These studies demonstrated that only gaps above the psychophysical gap detection threshold evoked significant MMN. This dissertation will focus on studies that used gaps in noise to evoke AEPs. However, neuromagnetic and gaps in tone studies will be considered in the discussion chapter.

2.5.1 Gap ABRs

Werner et al. (2001) recorded ABRs to gaps embedded in broadband noise; gap duration varied between 0-125ms. Gap detection thresholds were obtained based on the absence of peak V. Psychophysical gap detection thresholds were also obtained, and were similar to the threshold calculated based on the ABRs. The mean psychophysical gap detection threshold was 2.9ms while the electrophysiological gap detection threshold was 2.4ms.

In the second study conducted by Poth et al. (2001) the main focus was to investigate the effect of aging on ABRs. They used two bursts of broadband noise separated by 4, 8, 32 or 64ms to evoke ABRs. In all four gap durations peak V was detectable in responses to the first noise burst. In response to the second noise burst (after the gap), peak V disappeared for some subjects with gaps of 4 and 8ms duration. Older adults in this study exhibited diminished peak V compared to young adults with no latency shift.

2.5.2 Gap MLRs

The author is not aware of current literature which explores the use of gaps in white noise to evoke MLRs, with the exception of that published by the author (Alhussaini et al., 2015). Alhussaini et al. (2015) recorded MLRs to gaps in white noise implementing the deconvolution method. In this study, the effect of gap duration on the amplitude of MLRs was diminished as the gap becomes shorter. This effect is consistent with that of similar studies on the MLR and LLR amplitude.

In a neuromagnetic study, the existence of gaps responses was studied by recording magnetic middle latency fields (MAEF) (Rupp et al., 2002; 2004). Rupp et al. (2002) found that short gaps (6ms and 9ms) elicited recognizable MAEF responses. Analysis of MAEFs to gaps in noise showed that amplitudes increased with longer gaps (Rupp et al., 2002; Rupp et al., 2004). Additionally, it was shown that noise onset responses have larger amplitudes in contrast with noise offset responses. Moreover, the noise segment length preceding the gap has an influence on MAEF amplitudes; longer noise segments generate larger amplitudes (Rupp et al., 2004).

2.5.3 Gap LLRs

Cortical responses evoked by gaps in noise have been the subject of several studies; some of these studies have focused on the effect aging (Harris et al., 2012) while others focused on diseased populations (Michalewski et al., 2005). Michalewski et al. (2005) studied temporal processes in normal hearing subjects and subjects with auditory neuropathy. They recorded LLRs to gaps

embedded noise in which the gap duration varied between 2 and 50ms. They reported that normal-hearing subjects exhibited a detectable N1-P2 in response to gaps as short as 5ms, while subjects with auditory neuropathy required longer gap durations (10-50ms) to elicit a detectable N1-P2 complex.

Harris et al. (2012) conducted a study exploring the effect of age, attention and processing speed on LLRs using gaps in broadband noise. In their study, the stimulus was designed with 3, 6, 9, 12, 15ms gap durations were separated by 2 to 2.2 second white noise bands; each gap duration was presented in a sequence 250 times. Findings of this study were consistent with the pervious study in which the amplitude of LLRs was reduced by shorter gaps. They also reported an age effect on LLRs; older adults only had N1-P2 responses when the gap is equal or greater than 9ms while young adults had recordable responses with 6ms gap duration. Additionally, Palmer and Musiek (2014) have used LLRs to measure electrophysiological gap detection threshold in young and old adults and their finding on age effect were consistent with the Harris et al. (2012) study. Generally, in normal-hearing adults, amplitude of LLRs is reduced as the gap becomes shorter (Harris et al., 2012; Michalewski et al., 2005; Palmer and Musiek, 2013; 2014; Pratt et al., 2005).

2.6 Gap Onset/Offset Effect

Another study investigated the effect of the onset and offset of sound has utilizing tone bursts with durations between 1- 9.24 seconds (Hillyard & Picton, 1978). They reported a large N1-P2 in response to the onset and a significantly smaller in responses to the offset of the tone burst. The onset N1-P2 amplitude was also larger for short duration tone bursts, while the N1-P2 amplitude in response to the offset was reduced with shorter tone duration. In a later study using tone to record magnetoencephalography (MEG), the offset responses (N100m-Off) were reported to smaller than the onset (N100m-On) response. The spatial distribution of offset and the onset responses (within the A1 or where?) were distinct but relatively closely located to each other (Noda et al., 1998). In a different study using noise bursts instead of tones, Hari et al. (1987) found that MEG onset and offset responses (N100m) are very similar in amplitude and latency. They also reported that onset and offset responses sources were distinct but closely spatially located. In an animal study conducted on chinchillas to record AEPs invasively from the auditory cortex and inferior colliculus, offset responses to noise bursts was observed (Guo & Burkard, 2002).

All of the above mentioned studies focused on the onset and offset responses to a relatively long duration (longer than 1 second) sound (noise or tones). For gap detection paradigms, the gaps are typically short duration (less than tens of milliseconds) and the preceding and following noise segments are in hundreds of milliseconds. Therefore, there is an ambiguity on the contribution of the noise offset (gap onset) in the recorded LLRs to gaps in noise. Pratt et al.,

(2005) and Michalewski et al., (2005) have found that LLRs to gaps in noise showed a bifid N1 in responses to the gaps of 20ms or longer. The latency between the double N1 peaks was about 60ms regardless of the gap duration, which were up to 800ms. These findings rules out the possibility that the bifid N1 shape is caused by the overlapping of the onset and offset responses (Pratt, Bleich, & Mittelman, 2005). Furthermore, the same group has reported in a follow-up study that the N1 bifid shape is affected by the duration and intensity of the noise segment preceding the gap (Pratt et al., 2007). Additionally, they reported that the P50 is identifiable in responses to noise onset but absent to noise offset (Pratt et al., 2008).

2.7 Effect of Stimulus Type on Gap Responses

The design of the gap stimulus plays a significant role in the psychophysical measures as well as the electrophysiological measures in gaps testing paradigms. Some of the proposed psychophysical gap detection tests have used gaps in tones (Yalçınkaya et al., 2009) while other tests have used gaps in broadband noise (Musiek et al., 2005). Gap detection thresholds obtained using broadband noise in GIN test were lower than thresholds obtained using tones in the RGDT paradigm (Musiek et al., 2005; Yalçınkaya et al., 2009). Although gap detection thresholds may differ between different studies using different carrier sounds (noise or tones), Age related studies have demonstrated that thresholds are elevated in aged subjects comparing to normal hearing subjects regardless of if the stimulus tones or noise (Bertoli et al., 2002; Harris et al., 2012).

In addition, even the type of noise utilized for the gap testing paradigms has an influence on the study outcomes (Atcherson, Gould, Mendel, & Ethington, 2009). Atcherson et al. (2009) found that narrowband noise can elicit an N1 that has morphology different than that of an N1 elicited by gaps in broadband noise. Additionally, they found the behavioral gap detection thresholds change with respect to the center frequency of the narrow band noise. Lister et al. (2007) has explored this effect on cortical responses as well as psychophysical thresholds when using across-channel (spectrally different markers) instead of within-channel (spectrally identical markers). In the across-channel condition, they found that psychophysical thresholds are significantly higher than within-channel condition. Cortical responses were recordable in across-channel condition regardless of the gap duration (Lister et al., 2007).

CHAPTER 3: GOAL AND SPECIFIC AIMS

The main goal of this dissertation is to study the auditory evoked responses to gaps embedded in broadband noise. As mentioned in the background chapter, several gap detection tests have been proposed by several researchers. Additionally, auditory cortical responses to gaps in an ongoing sound have been recorded. However, some issues such as the gap offset response require more investigation. In the literature, the majority of gaps in noise studies were focused on recording cortical responses with only two studies focused on ABRs. We are not aware of any published electrophysiological study that uses gaps in noise to study MLRs and ASSRs. In order to achieve the general goal, we have the following specific aims:

We aimed to study all types of AEPs elicited by gaps embedded in broadband noise. Our objective was to record ABR, MLR and LLR as well as ASSRs. In order to record all these four types of auditory evoked responses, we will be relying on different processing techniques. To record LLR, we used the conventional averaging method. For early transient responses, we benefited from the deconvolution method to extract transient responses from overlapped responses due to high rate stimulation.

Moreover, we investigated and compared MLRs, LLRs and ASSRs in response to gaps embedded in broadband noise by looking at different factors: first, exploring the effect of gap duration on the AEPs morphology; second, studying the effect of stimulation rate on the AEP; and finally, investigating the influence of gap onset/offset on the transient evoked responses.

Additionally, as a secondary goal, we examined the feasibility of using 40Hz gaps to obtain gap detection thresholds. Palmer & Musiek (2014) proposed electrophysiological gap detection test (EGDT) based on recording LLRs and visually judging the presence of a response to gaps in noise. Our test was based on recording early transient response evoked by high rate gap stimuli, and then use the deconvolution method to have both the quasi ASSRs and ABRs-MLRs from a single recording session. We aimed to design an objective test that can provide gap detection threshold based on the (quasi ASSRs) in a relatively reasonable time suitable for clinical practice. We investigated if such an objective testing method based on early transient responses could estimate the psychophysical gap detection threshold reasonably. If confirmed, such an objective measure could be used to test temporal hearing acuity in behaviorally hard to test subjects such as newborns, infants and neurologically compromised patients.

CHAPTER 4: METHODS

Several experiments were undertaken to achieve the goals of this dissertation. The experimental design for many of the planned tests share similar recording setup and paradigm, data acquisition system used, and signal post processing. The methods and signal processing will be described in this chapter, and each experiment will be individually addressed in the next chapter. Any other additional methods or deviations from the common method will be described for that experiment.

4.1 Subjects and Recording

A total of twenty volunteer subjects (five female) participated in one or more of the experiments done in this dissertation. The mean age of the test population is 25.3 (St.Dev:4.1, range: 20-31). Each subject was administered a conventional pure-tone behavioral hearing test using a clinical grade audiometer (with SmartAud, Intelligent Hearing Systems (IHS) , Miami, FL). All subjects were assessed to have normal hearing (with thresholds ≤ 25dBHL at 0.25, 0.5, 1, 2, 4 and 8 kHz) and reported no neurological disorders. All participating subjects signed informed consent forms in accordance with the Institutional Review Board of the University of Miami. For privacy, each subject is referred to by an anonymous identification name (e.g. GAP0XX). Additional details are provided in Table 4.1 about subject's age and participation in each experiment. Justification of sample size used in the experiments is later discussed in the Appendix.

Testing was conducted in an acoustically and electrically isolated booth (Acoustic Systems, ETS-Lindgren Inc., Austin, TX). During testing, each subject was lying comfortably on a bed while watching a silent movie with closed captions. Subjects were instructed not to pay attention to the sound during signal acquisition, or to ignore it to the best of their ability. Additionally, to minimize muscle noise artifacts in the recorded signal, a single channel of the subject's real-time EGG signal was displayed on the same screen and the subject was asked to observe for sudden noise introduced by unintentional movement or muscle tension. The data acquisition session for each experiment was designed to last no longer than one hour in an effort to limit subject fatigue. However, if the experiment requires more than one session or the subject is participating in more than one experiment, the second session is done on a subsequent day.

TABLE 4.1.List of subjects identification names, ages, and study participation

#	Subject ID	Age	Experiment I	Experiment II	Experiment III	Experiment IV	Experiment V	Experiment VI
1	GAP002	29	√	√	√	√	√	√
2	GAP005	27	√	√				
3	GAP006	23	√	√	√	√	√	√
4	GAP007	22	√	√				
5	GAP010	29	√	√	√			√
6	GAP011	29	√	√	√	√	√	√
7	GAP012	20	√					
8	GAP013	20			√			
9	GAP014	20			√			
10	GAP015	23			√	√	√	√
11	GAP016	28			√	√	√	√
12	GAP017	21			√	√	√	√
13	GAP018	26						√
14	GAP021	20			√			
15	GAP023	30			√	√	√	√
16	GAP025	24						√
17	GAP026	31						√
18	GAP027	31						√
19	GAP028	30						√
20	GAP029	23						√
	Total	**25.3**	**7**	**6**	**11**	**7**	**7**	**14**
	S.D	**4.11**						
	Female subject							

4.2 Stimulus Generation and Presentation

Gap in noise stimuli are used for all experiments within this dissertation. In each experiment, variations in gap duration or the rate of stimulation are utilized to assess subject sensitivity to several parameters. The broadband noise used in all experiments was generated using the same specifications. All stimuli were generated using custom MATLAB scripts (Natick, MA, USA).To generate the noise, a random number generator was used to produce a uniformly distributed white noise signal. Then, the signal was digitally low pass filtered to 5 KHz (6^{th} order digital Butterworth filter).

The broadband noise signal was then modulated by inserting silent gaps into locations corresponding to the sequence designed for each experiment (discussed further later). However, in all experiments, the silent gaps maintained specific design constraints. The transition from noise to gap or from gap to noise was not instantaneous; the silent gap was gated with a slope of 1ms, for onset and offset (e.g. a 12ms gap has a 1ms linear ramp down, 10ms gap, and 1ms ramp up) (see Figure 4.4). In addition to noise gaps stimuli, 200μs clicks were also used in experiment V. Clicks were generated and calibrated using the IHS recording system.

All stimuli in all experiments were presented monaurally to the right ear at 70 dBSPL using insert ear phones (ER-3A, Etymotic Research, Elk Grove Village, IL). A reference table for the IHS-calibrated ER-3A transducer was used to define the approximate intensity of the generated stimuli. Additionally, we tested four normal hearing subjects to find their noise detection thresholds. All

four subjects were able to detect the noise at 30 dBSPL. Therefore, 70 dBSPL is about 40 dB above the sensation level, which was determined to be sufficient amplitude for our purposes.

Stimuli used in all experiments were presented with repetition rates of 0.5Hz, 1Hz, 5Hz, or 40Hz. Both isochronic and jittered sequences were used to acquire EEG responses to gap I noise sequences. The sweep length and the number of gaps presented in each sweep are summarized in Table 4.2. Stimulating at 40Hz, 8 gaps per 2048ms were presented in two modes (isochronic and low jittered). For the ischronic condition (40Hz ASSR), gaps were presented every 25.6ms (see Figure 4.2). For recordings using CLAD stimulus sequences, 40Hz QASSR stimuli were acquired using the low jittered sequence.

TABLE 4.2. Stimulus list showing rate of stimulation, sampling frequency, sequences loop length, and number of gaps presented in each sweep.

Stimulus name	presentation rate (Hz)	Sequence loop length	Sampling Frequency (Hz)	sweep length (sec)	number of gaps per sweep
0.5Hz	0.5	10000	5000	2.00	1
1Hz	1	5000	5000	1.00	1
5Hz	5	1024	5000	0.2048	1
40Hz QASSR	39.06	1024	5000	0.2048	8
40Hz ASSR	39.06	1024	5000	0.2048	8

4.3 EEG Signal Acquisition

A 2-channel evoked potential acquisition system (Intelligent Hearing Systems, Miami, FL, USA) was used for synchronously record EEG data and for stimulus presentation. Four gold cup electrodes were placed firmly on the skin using a medical grade conductive gel. The electrode placement montage was in accordance with the 10-20 system for vertex-to-mastoid configuration, (Ch.1: Cz-A2 and Ch.2: Cz-A1), with center of the forehead used as ground.

All results discussed in this dissertation are for data recorded ipsilaterally to stimulation, as shown in Figure 4.1. Raw EEG data were obtained with the following recording parameters: gain of 100,000x, with analog band-pass filter at acquisition for 1-1500Hz (6dB/oct) and with sampling rate of 5000 samples /s. The raw EEG was stored to disk for offline processing and analysis.

4.4 Averaging, Processing and Deconvolution

Offline post processing was performed using custom MATLAB software utilities. Signal averaging was performed with a rejection threshold of 80μV to remove unwanted large noisy artifacts. The signal-to-noise ratio (SNR) was calculated based on the plus-minus average method (Wong and Bickford, 1980).

SNR for all traces was estimated for the full sweep length (specified in Table 4.2) of the trace. However, in some cases, SNR was estimated over the first 500ms of the response. The SNR window will be specified where necessary in the discussion when it is used.

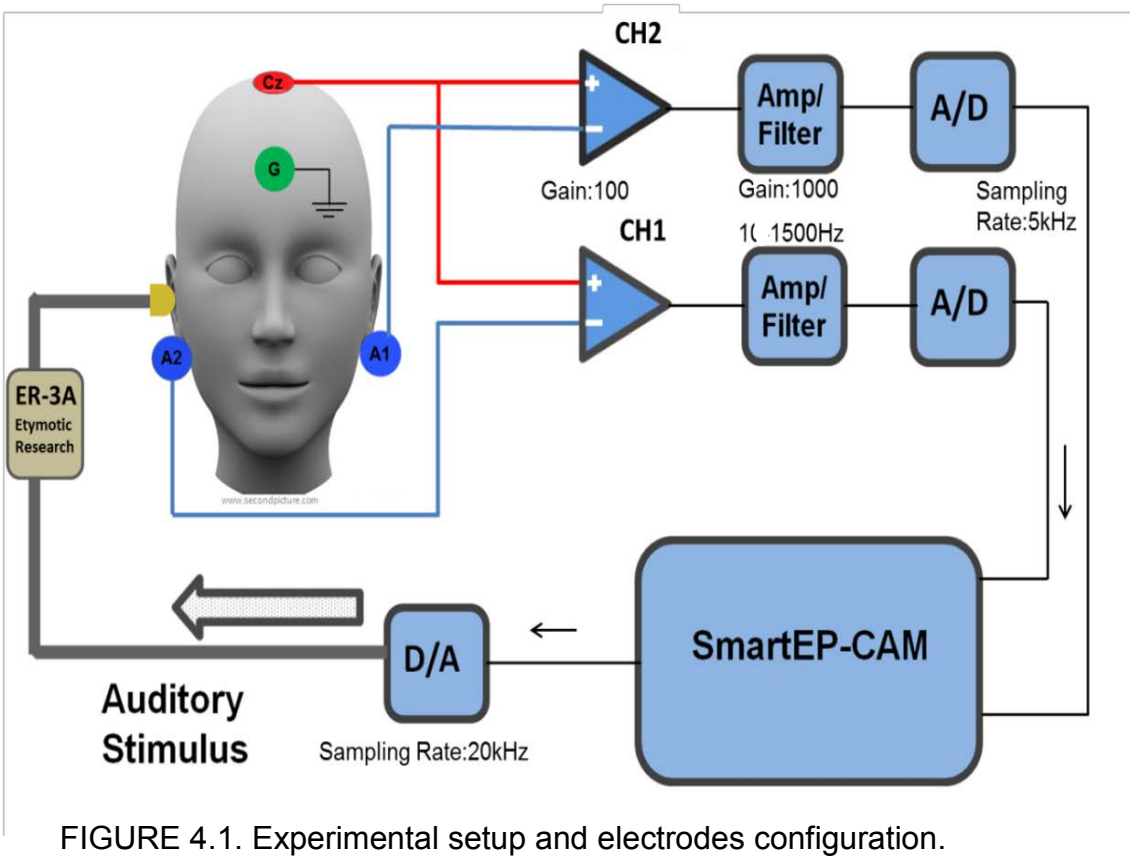

FIGURE 4.1. Experimental setup and electrodes configuration.

The deconvolution method was utilized for signals acquired with 40Hz CLAD sequence in experiment I, II and VI (Delgado & Ozdamar, 2004; Ozdamar & Bohórquez, 2006). The low-jitter CLAD sequence used is shown in Figure 4.2. Figure 4.2 compares between the low jittered sequence and the isochronic sequence used in experiment VI. Details about the deconvolution method are in section 2.3.3 in Chapter II.

First, the 40Hz EEG responses are averaged to obtain a single sweep representation for the EEG with high SNR, then the deconvolution procedure is applied to the Quasi ASSR (QASSR), as shown in Figure 4.3. Comparison

between 40Hz ASSR and 40Hz QASSR is discussed in the results of experiment VI for validation purposes.

Initially, all responses are processed using only the preset acquisition filters (1-1500 Hz). However, to improve signal quality in some cases a band pass 2nd order zero-phase Butterworth filter (1-30Hz) was used to superimpose a smoothed representation of the signal on the top of the original signal. The reason for applying the band-pass filter (1-30Hz) is to provide a fair comparison to some of the published studies on gaps in noise for LLRs (Harris et al., 2012; Michalewski et al., 2005; Palmer and Musiek, 2013; 2014; Pratt et al., 2005). Additionally, the 1-30Hz filter facilitates late latency response peak detection, but in some cases may diminish ABR and MLR peaks. Therefore both full bandwidth and filtered (1-30Hz) traces will be discussed in experiments III and IV results.

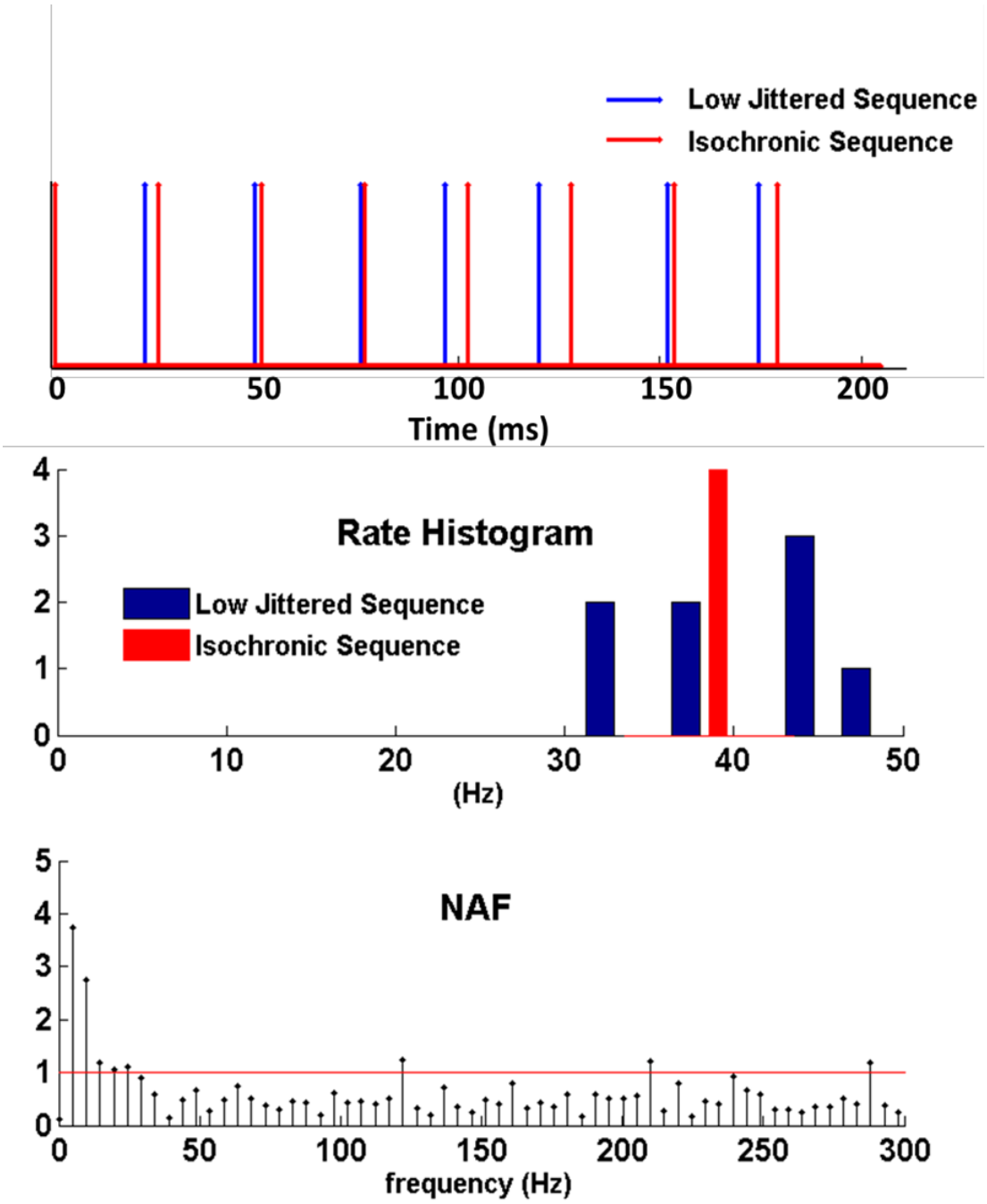

FIGURE 4.2. Comparison of the isochronic and low-jittered CLAD stimulus paradigms. (Top) Temporal occurrences of each sequence. (Middle) comparison of isochronic and low-jittered rate histograms. (Bottom) Noise Amplification Factor (NAF) of the low-jittered sequence used in this study.

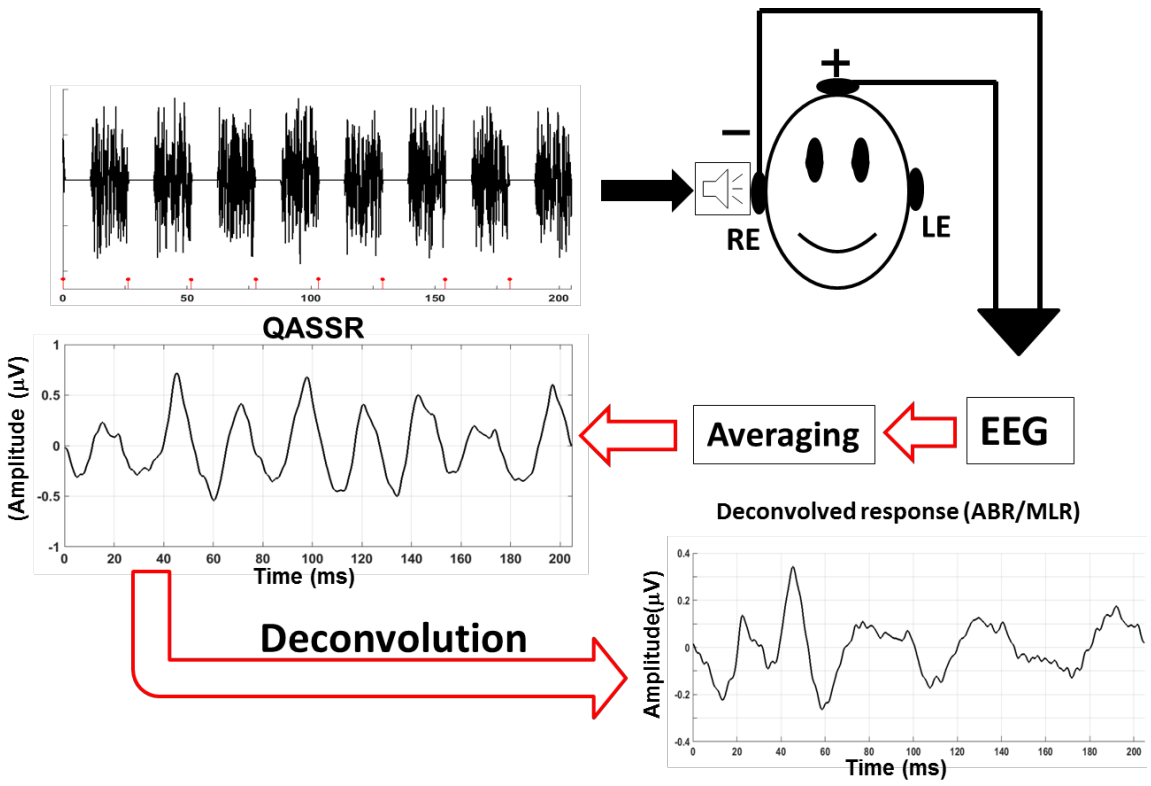

FIGURE 4.3. Experimental setup and illustration of the deconvolution procedure for the 40Hz CLAD-acquired response.

4.5 Behavioral Gap Detection Thresholds

In experiment I and II, a Behavioral Gap Detection Threshold (BGDT) test was performed. In order to obtain BGDTs, 13 acoustic stimuli were used with gap durations varying between 0ms (no gap) to 12ms. Each stimulus was contained in a 12 second noise segment containing 5 gaps of the same duration (see Figure 4.4). Each condition out of the 13 gaps was repeated 6 times in a random fashion. Subjects were instructed to press a push button for each detected gap in the noise segment. A gap threshold was assigned to each subject based on

≥50% successful gap detection attempts (three or more successful gap detection out of six).

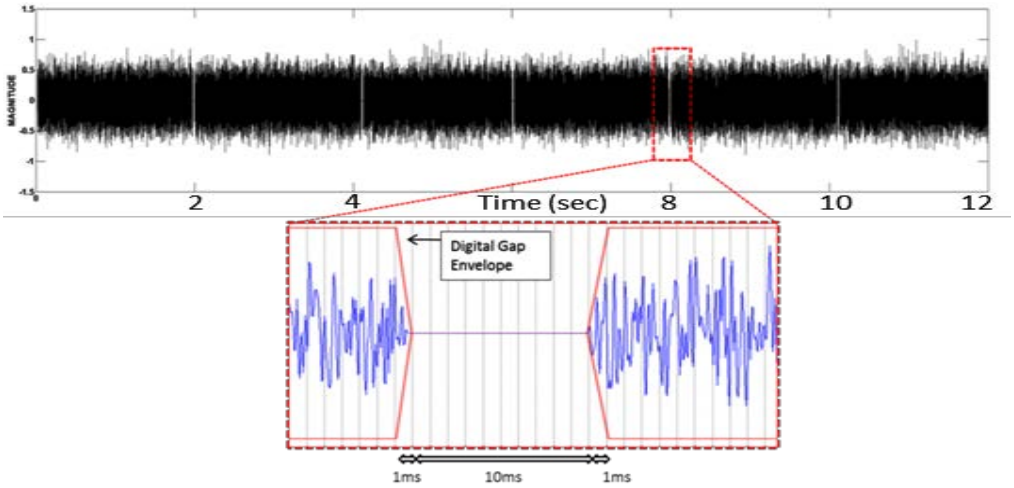

FIGURE 4.4. Example of 12ms gap stimulus used to assess Behavioral Gap Detection Threshold (BGDT). Five gaps of the same duration are present in this signal as observed. The transition from noise to gap or gap to noise is 1ms slope in all cases.

CHAPTER 5: EXPERIMENTS

5.1 Experiment I: Electrophysiological Responses to Gaps in Noise at Different Stimulation Rates

5.1.1 Objective

The first experiment was designed to investigate the effect of stimulation rate on the characteristics of responses evoked by short gaps in noise. MLR and LLR components were investigated using three different rates: 0.5Hz, 5Hz and 40Hz. Responses to 0.5Hz and 5Hz stimulation rates were acquired using standard averaging, and transient responses to 40Hz stimulation were obtained by utilizing the Continuous-Loop Averaging Deconvolution (CLAD) method (Delgado & Őzdamar, 2004; Őzdamar & Bohorquez, 2006). Finally, Behavioral Gap Detection Threshold (BGDT) was obtained from all participating subjects. The objective of this experiment was to score responses for the presence of these components, and evaluate rate-related response

5.1.2 Study Description

Seven right-handed young adults, aged between 19-29 years, participated in our study (see table 4.1).

Three rates (40, 5 and 0.5Hz) and two gap durations (9 and 12ms) were used in this experiment. For 40Hz stimuli, the gap onset intervals were slightly jittered so single sweep MLRs can be extracted using the frequency domain deconvolution (CLAD) method (Őzdamar & Bohorquez, 2006). For 5Hz stimuli,

the gap onset intervals were equally spaced. Lastly, in 0.5Hz stimuli, gaps were distributed in noise every 2 seconds. Illustration of the three stimuli and the gap design envelope are shown in Figure 5.1.Finally, BGDTs were obtained from all subjects using the methodology explained earlier in chapter 4.

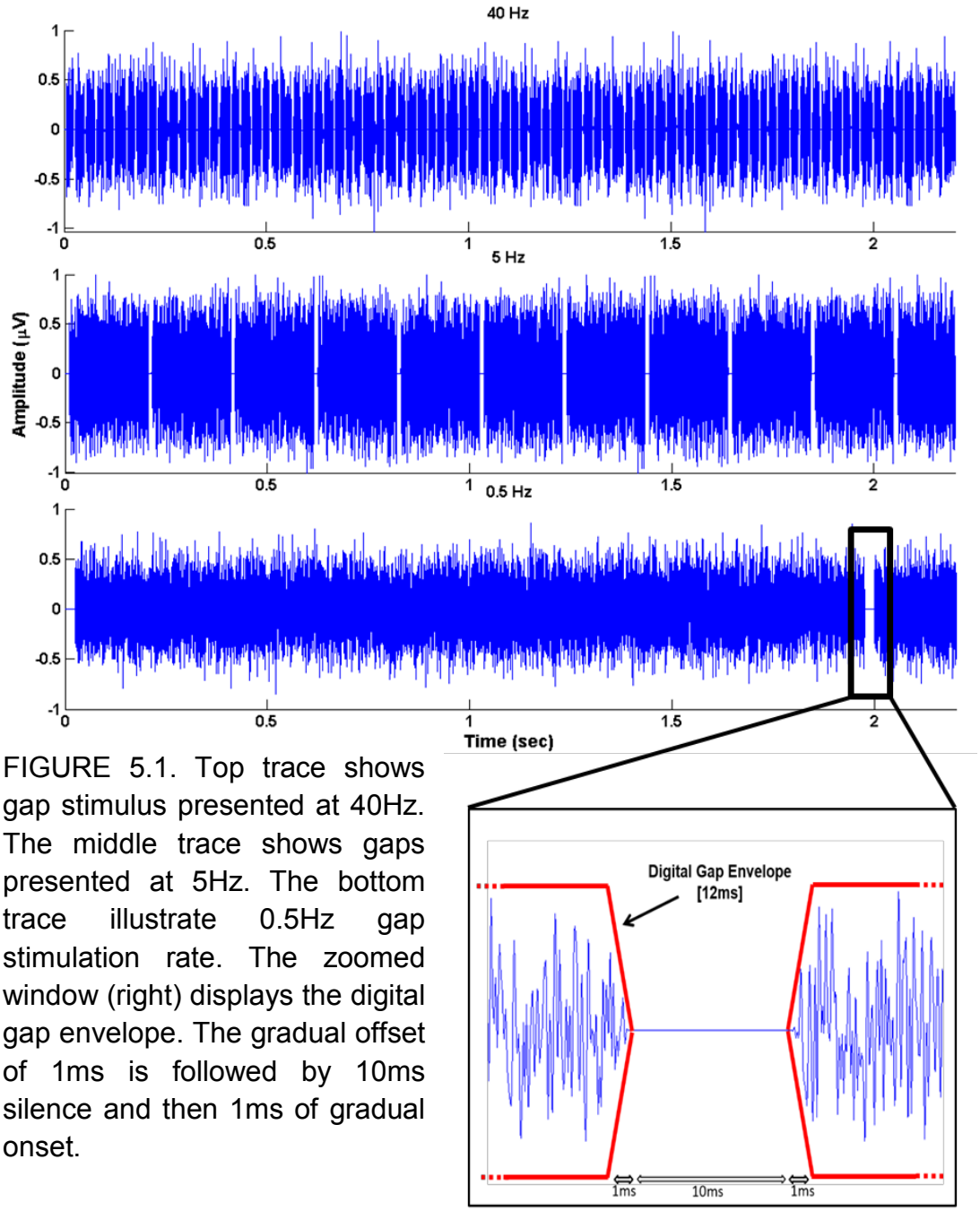

FIGURE 5.1. Top trace shows gap stimulus presented at 40Hz. The middle trace shows gaps presented at 5Hz. The bottom trace illustrate 0.5Hz gap stimulation rate. The zoomed window (right) displays the digital gap envelope. The gradual offset of 1ms is followed by 10ms silence and then 1ms of gradual onset.

5.2 Experiment II: Objective Analysis of Early Auditory Responses Elicited by Gaps in Noise

5.2.1 Objective

In the second experiment, a 40Hz CLAD sequence was utilized to obtain high-rate transient responses to gap stimuli. The transient responses (deconvolved ABR and MLR) are analyzed in an effort to objectively determine gap detection thresholds. By using the deconvolution method, we were able to acquire both early transient responses (ABR/MLR) as well as the QASSR in one recording session. Objective gap detection thresholds (OGDT) were obtained by using the standard clinical down-up threshold protocol as described in Lachowska et al., (2012). To validate OGDTs, behavioral gap detection thresholds (BGDTs) were also obtained from all subjects. This work was discussed in detail in "Objective Analysis of Early Auditory Responses Elicited by Gaps in Noise" (Alhussaini et al., 2015). The following sections are a summary of the mentioned article.

5.2.2 Study Description

Six young subjects participated voluntary in this study (see table 4.1).

In total, 11 stimulus sequences were generated with gap durations ranging from 0ms (no gap) to 12ms. All gaps within a single sequence were the same duration. Additionally, BGDTs were obtained using the method explained earlier in chapter 4.

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5.3 Experiment III: Onset/Offset Effect on LLRs

5.3.1 Objective

For the third experiment, the objective was to evaluate whether the gap-evoked LLR is evoked primarily by the onset of the noise (gap offset) or there is a contribution from the offset of the noise (gap onset). To address this question short and long gap durations were used to elicit LLRs. Unlike the previous experiment, in the current one we evoke AEPs by using one fixed stimulation rate (1Hz) since the rate effect is not the major question of this experiment. Five Gaps varied in duration between 12ms and 300ms were used. By using large gaps (e.g. 300ms gap duration); the characteristic LLR components of P1-N1-P2 are evoked by both the onset and the offset of the noise without overlapping of the two responses. Consequently, by shortening the gap from 300ms to 12ms, we will inspect the change of the P1-N1-P2.

5.3.2 Study Description

Eleven right-handed young adults, aged between 20-30 years (mean age is 24.5 years), (see table 4.1).

As described above, a 1 second sequence of background of white noise is used, and then then modulated by inserting 1ms linearly gated silent gaps of either 12ms or 300ms within the sequence, as shown in figure 5.2. Five gaps were used for generating sequences: 12, 25, 50, 150 and 300ms. Each sequence contained only a single gap length, and the gap occurred at the end of

the sequence. Finally, the 1 second noise and gap sequence was played on loop for the desired number of sweeps repetition.

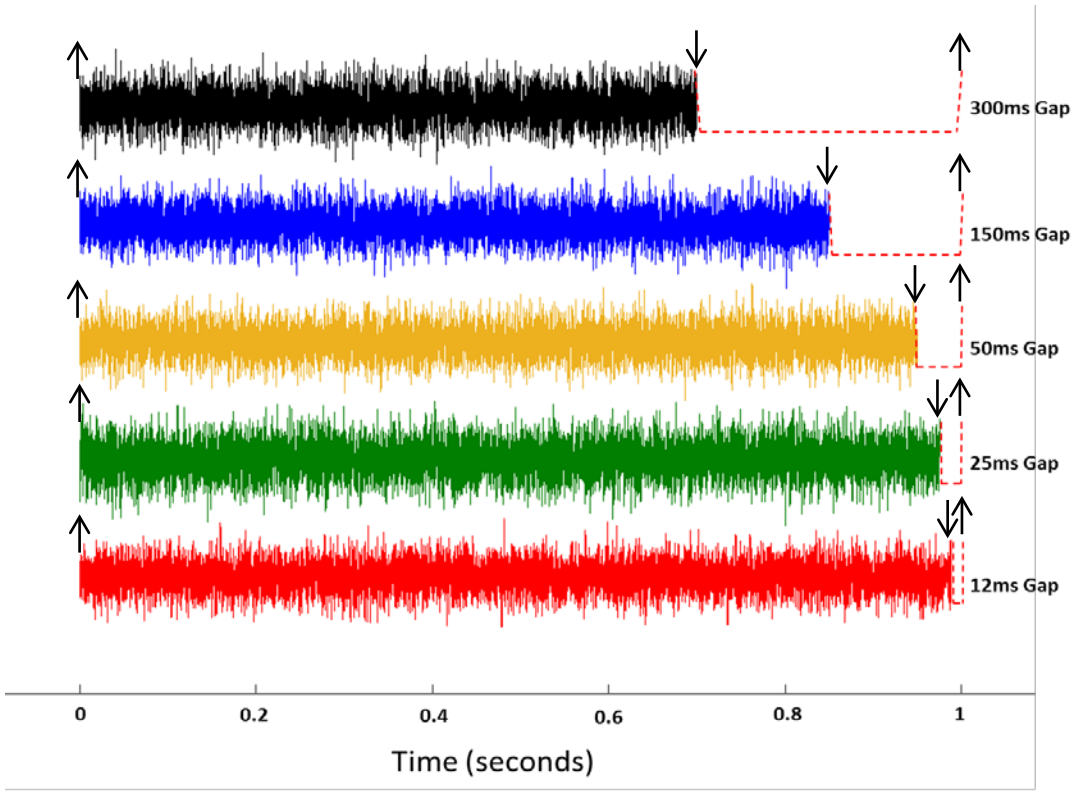


FIGURE 5.2. One second long Stimuli with gaps ranging from 12ms (bottom) to 300ms (top).Arrows used as indicators for noise onset and offset.

5.4 Experiment IV: Onset/Offset Effect on LLRs (extended)

5.4.1 Objective

In this experiment, LLRs evoked by gaps using the same method in experiment three. However, for experiment three, five set gap durations were used (12, 25, 50, 150 and 300ms). For this extension, five extra five gap durations were added in order to more finely evaluate the effect of gap duration in LLR responses. The additional gap durations of 6, 9, 100, 200 and 250ms were added to complete a total of ten gap durations.

5.4.2 Study Description

Seven out of the eleven subjects participated in experiment III participated in this experiment. They were young adults, aged between 21-30 years (mean age is 24.8 years) (see table 4.1).

Same method used in experiment three was used in this experiment to generate the ten stimuli. Stimuli were gap in noise stimuli with gap duration ranging from 6ms to 300ms. The gap durations were: 6, 9, 12, 25, 50, 100, 150, 200, 250, and 300ms presented in 1 sec segment of noise. The stimulation rate is 1 per second (1Hz).

5.5 Experiment V: Comparison between Double Clicks Reponses and Gaps Responses

5.5.1 Objective

For experiment V, the morphology of AEPs evoked by different durations of gaps in noise is compared to the AEPs evoked by double clicks. In previous studies, we found that 25ms gap elicited the largest N1-P2 complex. Additionally by using 300ms gap, we were able to see the noise onset response apart from the noise offset response. Therefore, 25ms and 300ms gap duration was chosen to be compared to clicks separated by either 25ms or 300ms. Here, we will assume that the 25ms double click will evoke a convolved response of the two clicks. Conversely, the two clicks separated by 300ms will evoke two distinct responses.

5.5.2 Study Description

Total of seven young volunteers (21-30 years mean age is 24.8 years) (see table 4.1 for details).

Two sets of sound stimuli were used in the experiments. For the first condition (gaps), a random number generator was used to produce a uniformly distributed low-pass filtered white noise signal. The noise signal was then modulated by inserting a gap of 300ms for the first stimulus and 25ms gap for the second stimulus (see figure 5.3). For the second condition (clicks), two rarefaction clicks separated by 300ms and 25ms were used. The clicks' temporal locations corresponded to the offset and the onset of the gaps in the first

condition's stimuli. The effective repetition rate of both the gap or click condition is 1 Hz.

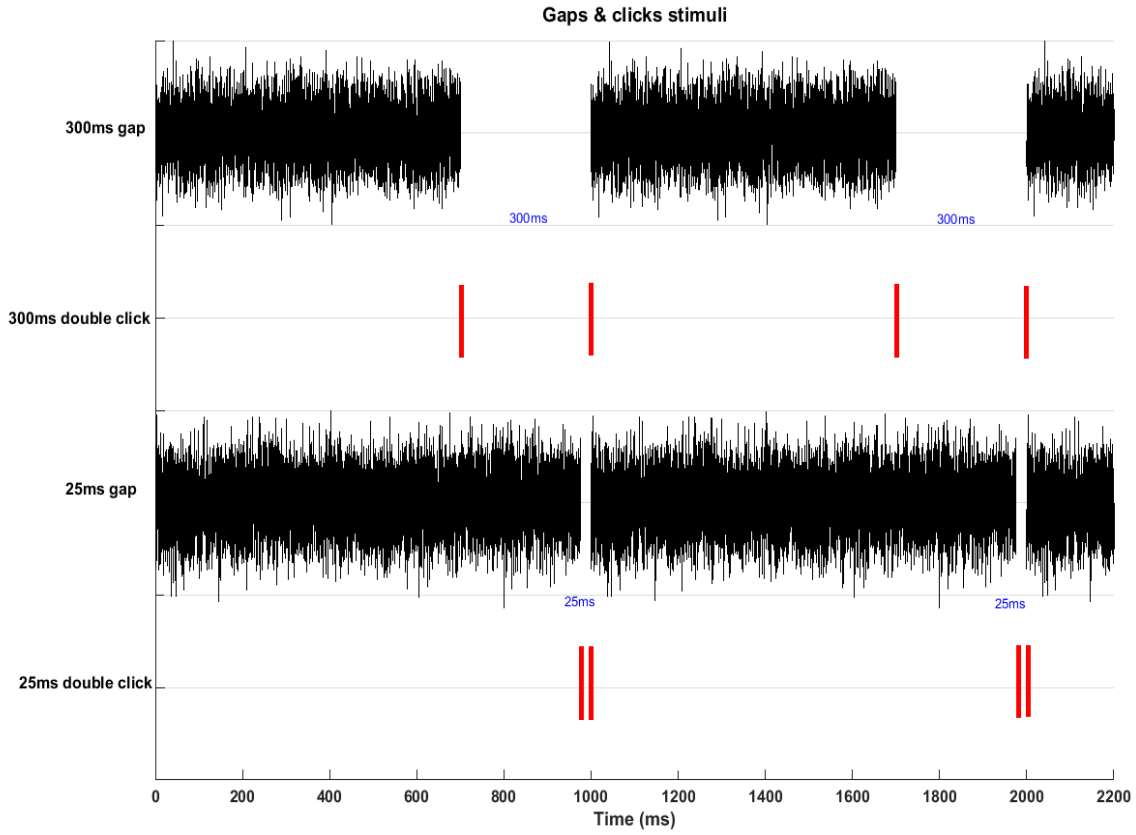


FIGURE 5.3. Top plot represents stimuli of 300ms gap (black) and double click separated by 300ms (red). Bottom plot represents 25ms gap and double click separated by 25ms.

5.6 Experiment VI: Auditory Transient and Steady-State Evoked Potentials to Gaps in Noise

3.6.1 Objective

For experiment VI, the morphology of AEPs to a single duration gap in noise stimulus is compared for different stimulation rates. The effect of rate on the characteristics of electrical responses evoked by short gaps (12ms) is studied for MLR, LLR and the ASSR. Four stimulation rates are used: 0.5, 1, 5 and 40Hz. Characteristic peaks and latencies of transient responses are tabulated and discussed, as well as the magnitude and phase of the ASSR.

5.6.2 Study Description

Total of 14 volunteers (ages 20-30, mean 26.8), see table 4.1 for details.

In total, five stimuli were used in this experiment (0.5Hz, 1Hz, 5Hz, 40Hz QASSR and 40Hz ASSR). In 0.5Hz stimulus, gaps were distributed in noise every 2.00s. For 1Hz stimulus, gaps were distributed every 1.00s. For 5Hz stimuli, the gap onset intervals were equally spaced (0.204s). All stimuli used in this experiment are illustrated schematically in Figure 5.4.

For 40Hz stimuli, there were two stimuli generated, in the first one, the gap onset intervals were fixed to produce 40Hz ASSRs. In the second 40Hz stimulus, the gap onset intervals were slightly jittered so single sweep ABR-MLR can be extracted using the frequency domain deconvolution (CLAD) method (Őzdamar & Bohorquez, 2006) as illustrated earlier in Figure 4.3.

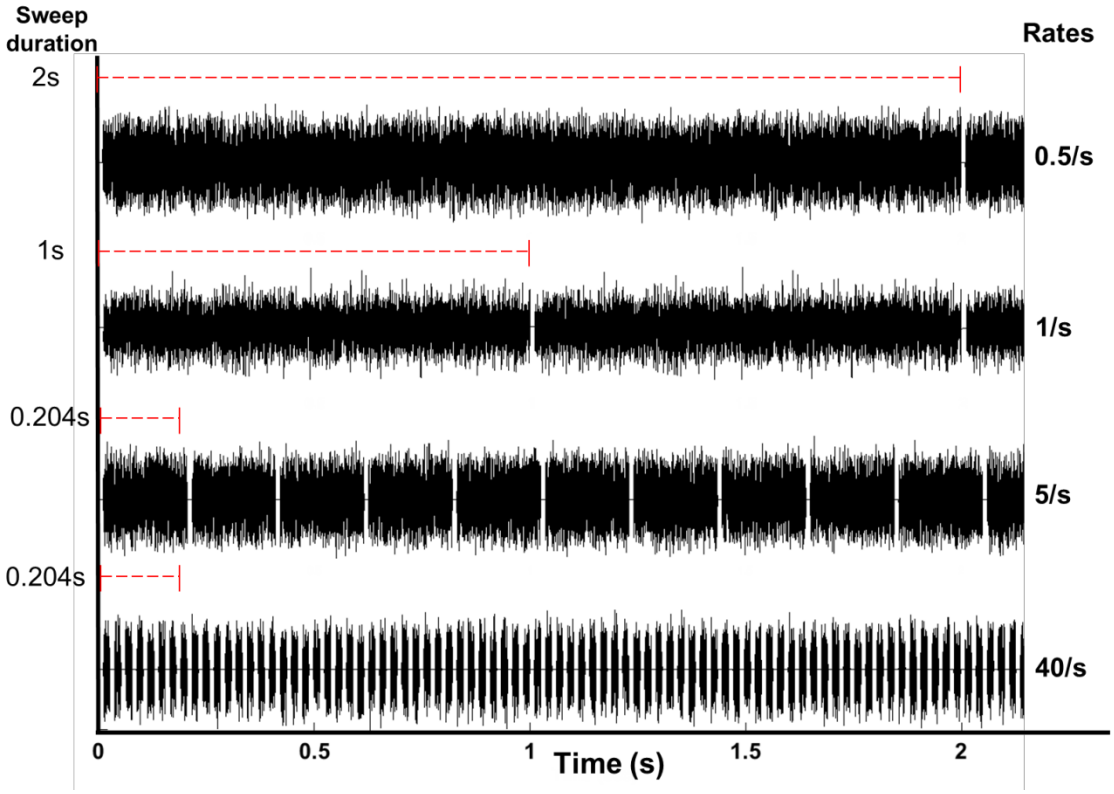


FIGURE 5.4. Four gap in noise stimuli of different rates (0.5, 1, 5 and 40Hz)

CHAPTER 6: RESULTS

This chapter presents results obtained during the experiments outlined in methods explained in chapters four and five, and to achieve the specific aims presented in chapter three. Generally, the experiments were designed and executed systematically in order to integrate the findings of the first experiments to motivate each of the following experiments, and in order to address the boarder goals of the response of the auditory system to gaps in noise. Consequently, we will see for example that the results of experiment four is just an expansion in the number of gap durations used in experiment three.

6.1 Experiment I: Electrophysiological Responses to Gaps in Noise at Different Stimulation Rates

In this section, responses to three stimulation rates using two gap durations (9ms and 12ms) are shown. First, AEPs in response to gaps in noise with an inter-gap stimulation interval of 2 seconds (0.5Hz) are presented. Responses to gaps presented at faster stimulation rates of 5Hz and 40Hz are also discussed. For the 40Hz responses, the CLAD method was used to obtain deconvolved responses from the overlapped responses caused by high stimulation rate. In addition to the three evoked responses to different stimulation rate, behavioral gap detection thresholds were also obtained from all subjects in this experiment for direct comparison between methods. As described in the

method chapter, 0.5Hz stimulation rate stimuli were utilized to generate 12 second long stimulus sequences.

6.1.1 Electrophysiological Responses:

Population grand average results (N=7) for 0.5, 5, and 40Hz responses are shown in figure 6.1. The top trace in Figure 6.1 shows population averaged late latency responses to 0.5Hz stimulation. The 0.5Hz LLRs were generally characterized by presence of P1, N1, and P2 components, and clearly showed the presence of all three principal waves, P1, N1 and P2. Statistical analysis of peaks latency and amplitudes are shown in figure 6.2.

All responses in this experiment were averaged so that the noise offset is at *t*=0s (or gap onset). Therefore, we generally refer to the gap onset as the stimulus onset. All latencies are described as they appear after stimulus onset. The latency of all the three principal peaks P1, N1 and P2 were similar across subjects. For the 12ms gap, the mean latency of P1 is 50ms (Std. Dev: 6.36ms). While for 9ms gap, the mean P1 latency was 54ms (Std. Dev: 7.4ms). The mean N1 latency for 12ms and 9ms gaps were 105ms (Std. Dev: 6.5ms) and 97ms (Std. Dev: 9ms) respectively. Lastly, the mean P2 latencies for 12ms and 9ms gaps were 162ms (Std. Dev: 12ms) and 169ms (Std. Dev: 10ms) respectively.

For the 0.5Hz condition, amplitudes were measured as P1-N1 and N1-P2. The mean P1-N1 amplitude for 12ms gap was 1.77μV (Std. Dev: 0.74) and 1.56μV (Std. Dev: 0.48) for 9ms gap. For N1-P2, the amplitude was 3.46μV (Std. Dev: 1.38) for 12ms gap and 3.01μV (Std. Dev: 0.74) for 9ms gap.

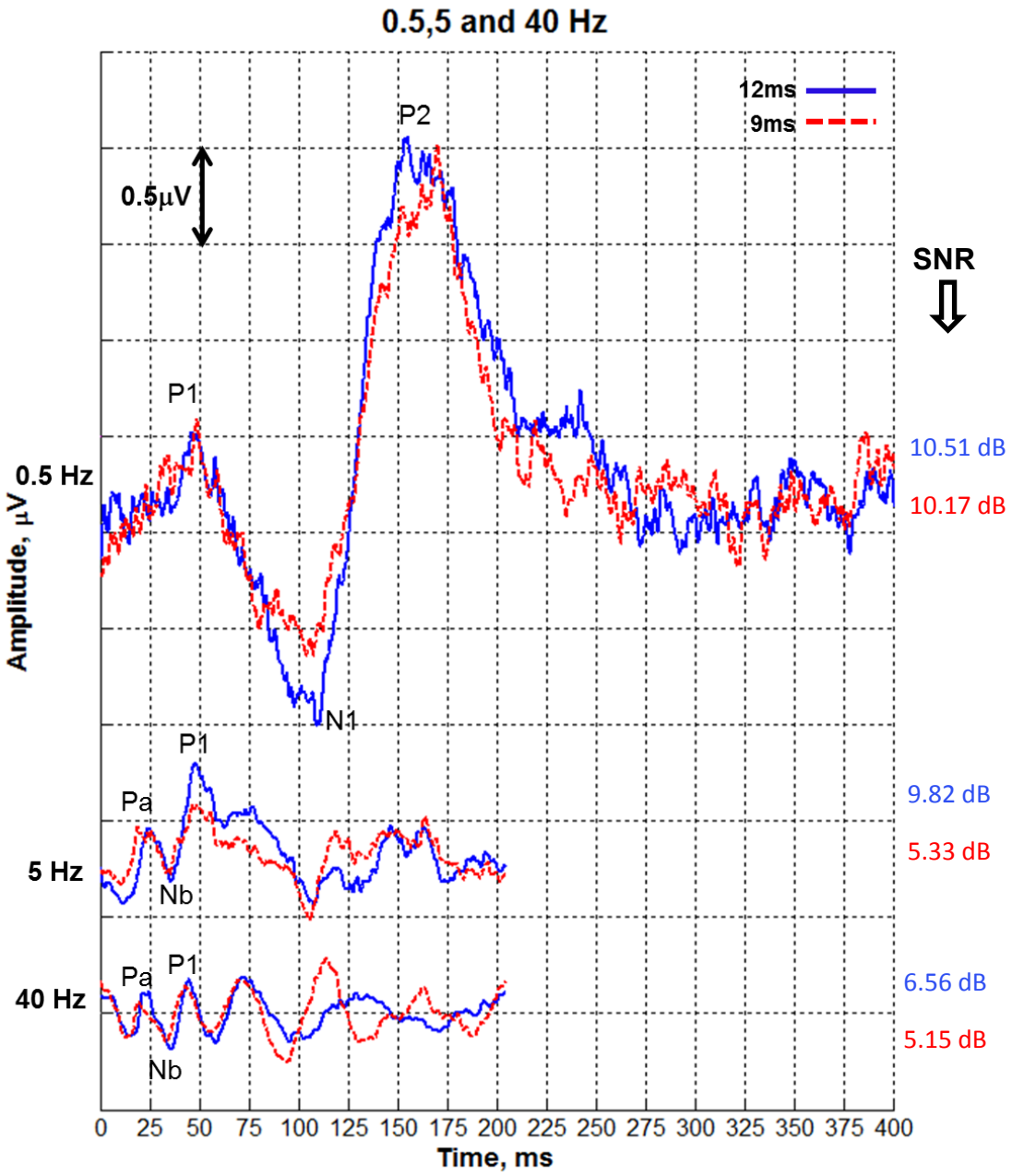


FIGURE 6.1. Grand average (7 subjects) responses to 0.5Hz and 5Hz isochronic gap in noise stimulation are show in the top and middle traces, respectively. The lower trace shows grand average results for deconvolved responses to 40Hz stimulation rate. The LLR for 0.5 Hz has peaks P1, N1, and P2 are labeled. The 5 and 40Hz MLR components are labeled. For all responses, the blue line represents 12ms gap responses while the red dotted line represents 9ms gap response. SNR is shown based on the color on the right for each trace. For the 0.5Hz responses, SNRs were calculated for the first 500ms only.

Grand population average of early responses for 5Hz and 40Hz stimuli are shown in figure 6.1. The 5 Hz Responses were characterized by three negative and two positive peaks. These components were clearly identified in the MLR recordings as shown in figure 6.1. The morphology of deconvolved responses to 40Hz stimuli is characterized by four negative and four positive peaks, indicating oscillating waves. The averages and the standard error of peak to peak amplitudes and latencies of all the 0.5Hz and 5Hz gap response components are shown in Figure 6.2.

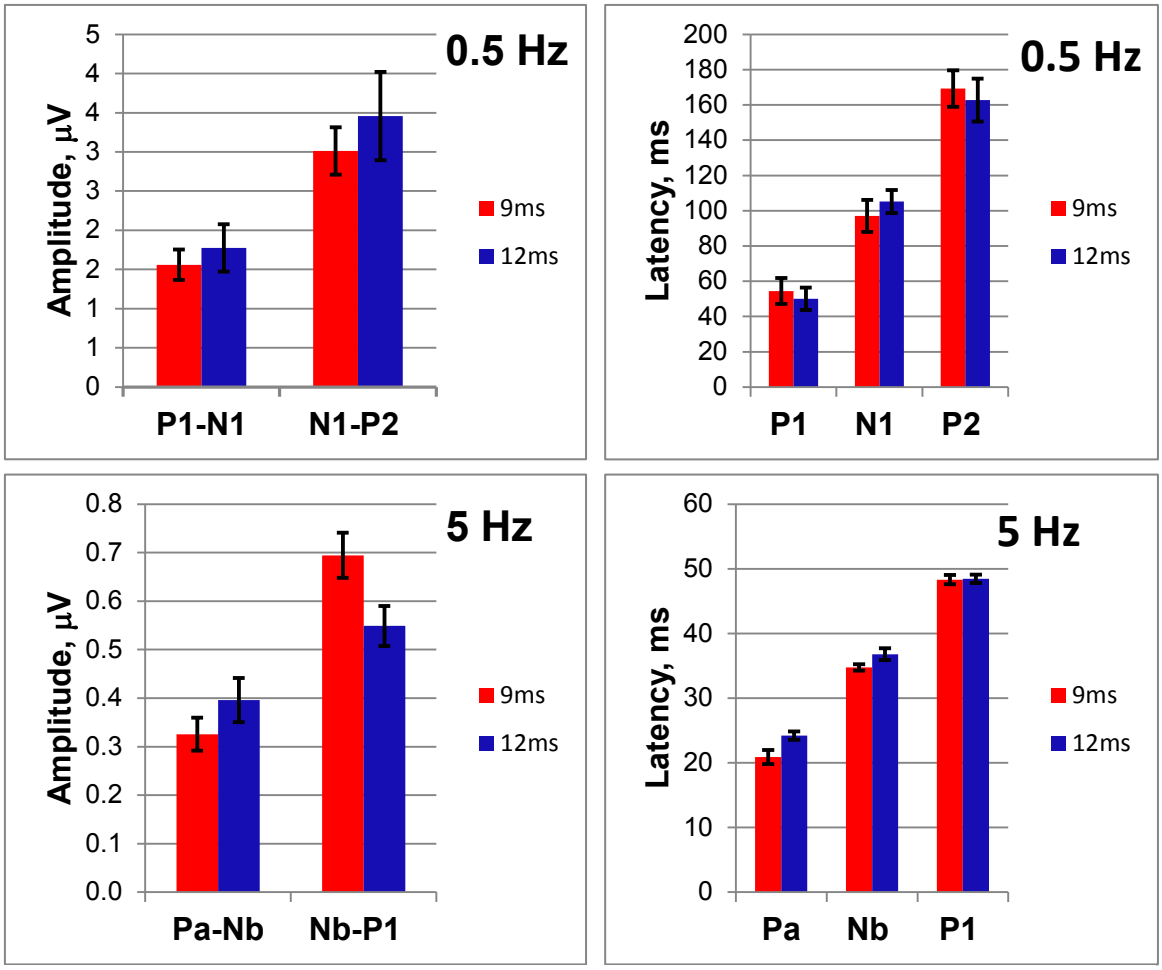


FIGURE 6.2. (Top) statistical analyses (mean with standard error bars) are shown in bar graphs for LLRs peaks (amplitude, left & latency, right) in response to 0.5Hz stimuli. (Bottom) mean with standard error bars are shown for MLRs peaks (amplitude & latency) in response to 5Hz.

Results of the statistical analysis of 0.5Hz responses showed that the effect of gap duration was not significant on P1, N1 and P2 latencies ($p < 0.05$). Similarly, for 5 and 40Hz results, P1 latency was not affected by gap duration. On the other hand, using 2-way ANOVA to analyze the effect of rate on P1 latency showed significance ($p > 0.05$) as illustrated in Figure 6.3.

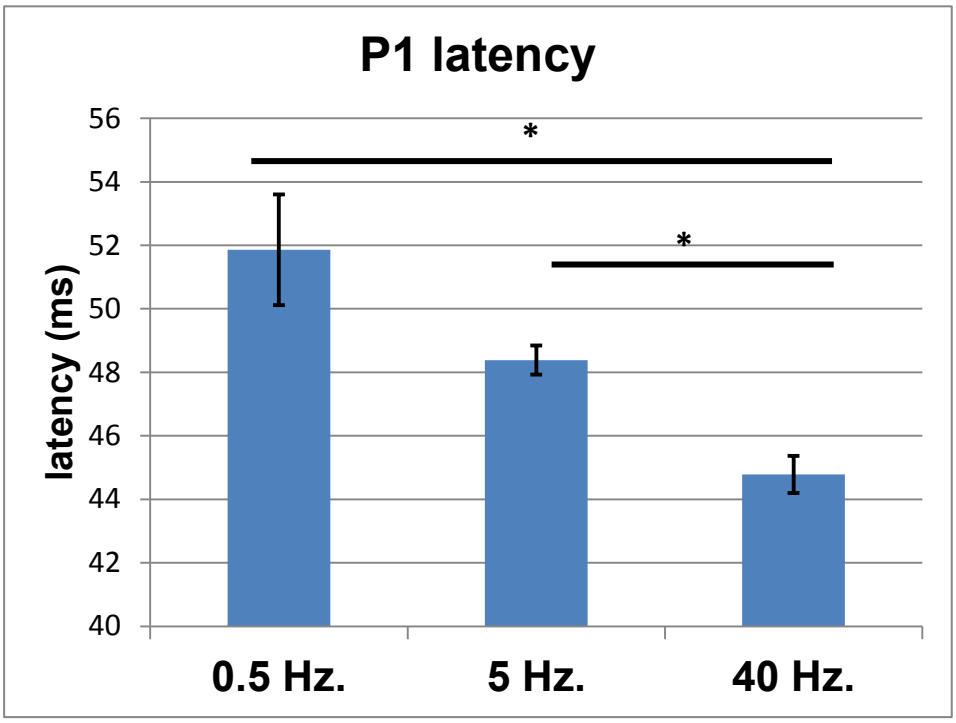
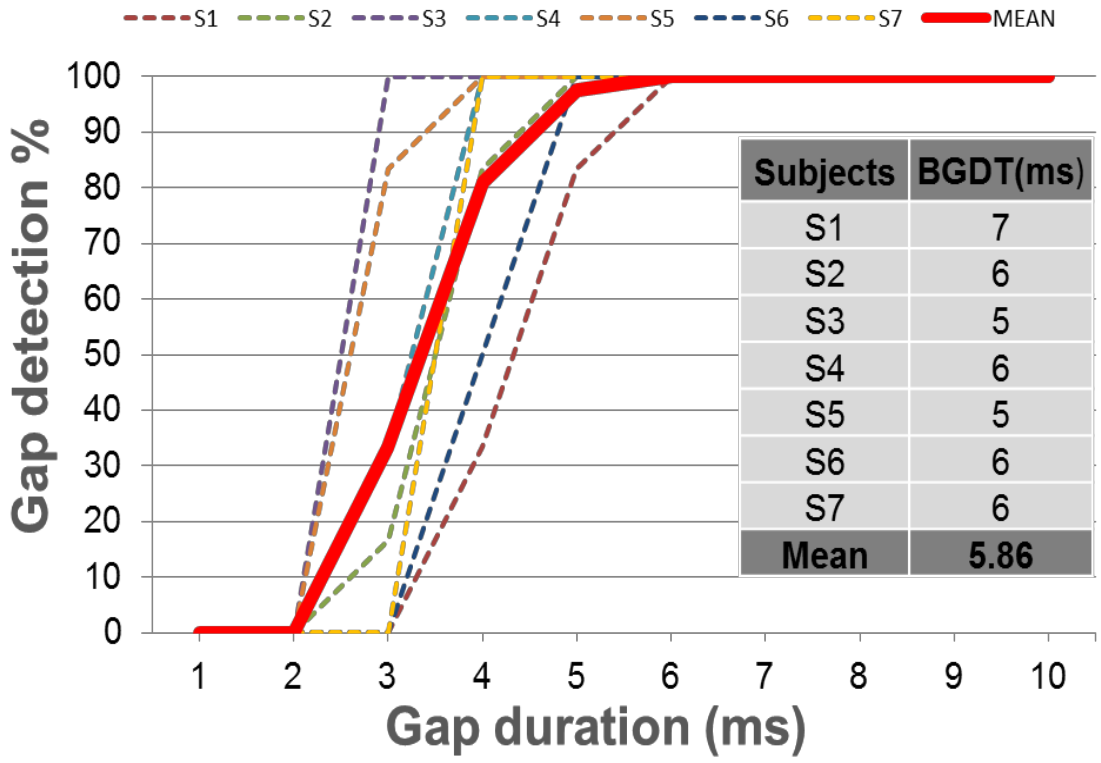


FIGURE 6.3. (Top) mean and standard error bars for P1 latency in response to 0.5Hz, 5Hz and 40Hz stimuli. Statistical significance is indicated with stars (*, $p<0.05$). Significant difference between 40Hz and 5Hz and between 40Hz and 0.5Hz are shown.

6.1.2 Behavioral Gap Detection Thresholds (BGDTs)

BGDTs were obtained from all 7 subjects with lowest BGDT of 5ms and the highest is 7ms. BGDTs were calculated based on 3 or more successful attempts of gap detection out of six (for BGDT ≥ 50% detection). Figure 6.4 illustrates gap detection percent as a function of gap duration, while the table in Figure 6.4 represents BGDTs of each individual subject with the mean BGDT of the entire study population.



Subjects	BGDT(ms)
S1	7
S2	6
S3	5
S4	6
S5	5
S6	6
S7	6
Mean	**5.86**

FIGURE 6.4: The mean gap detection percent illustrated as a function of gap duration. Behavioral Gap Detection Thresholds (BGDTs) are shown in the table; thresholds are determined based on (≥50%) gap detection out of 6 attempts.

6.2 Experiment II: Objective Analysis of Early Auditory Responses Elicited by Gaps in Noise

The primary aim of this experiment was to investigate the feasibly of using 40Hz noise gaps to evoke AEPs. In experiment I, responses to 40Hz gap stimulation were recorded utilizing two gap durations (9ms and 12ms). In this experiment, the effect of gap duration on ABR/MLR by using 11 gap durations ranges between 0 to 12ms was assessed. Additionally, the Objective Gap Detection Thresholds (OGDT) was assessed using the Quasi Auditory Steady-State (QASSR) response elicited by the same 40Hz stimuli and by implementing the Lachowska et al., (2012) objective detection method (see chapter 4). Finally, objective and behavioral gap detection thresholds are compared for all the study population.

6.2.1 Transient Responses

Deconvolved transient responses (ABR/MLR) were obtained from all six subjects. Figure 6.5 shows a grand population average for all gap durations (0ms-12ms). All responses were averaged with noise offset (or gap onset) to be at t=0s. In general, amplitudes of characteristic peaks were reduced as the gap becomes shorter while latencies remain stable. Peaks for response to gaps below 5ms are no longer clearly identifiable. However, peaks latencies are different from those elicited by conventional clicks or tones.

The gap responses for 12ms (top trace in Figure 6.5) were large in amplitude in comparison to the shorter duration gaps. The response is

characterized by three negative peaks and three positive peaks; with the positive peak around 20ms is the most prominent one.

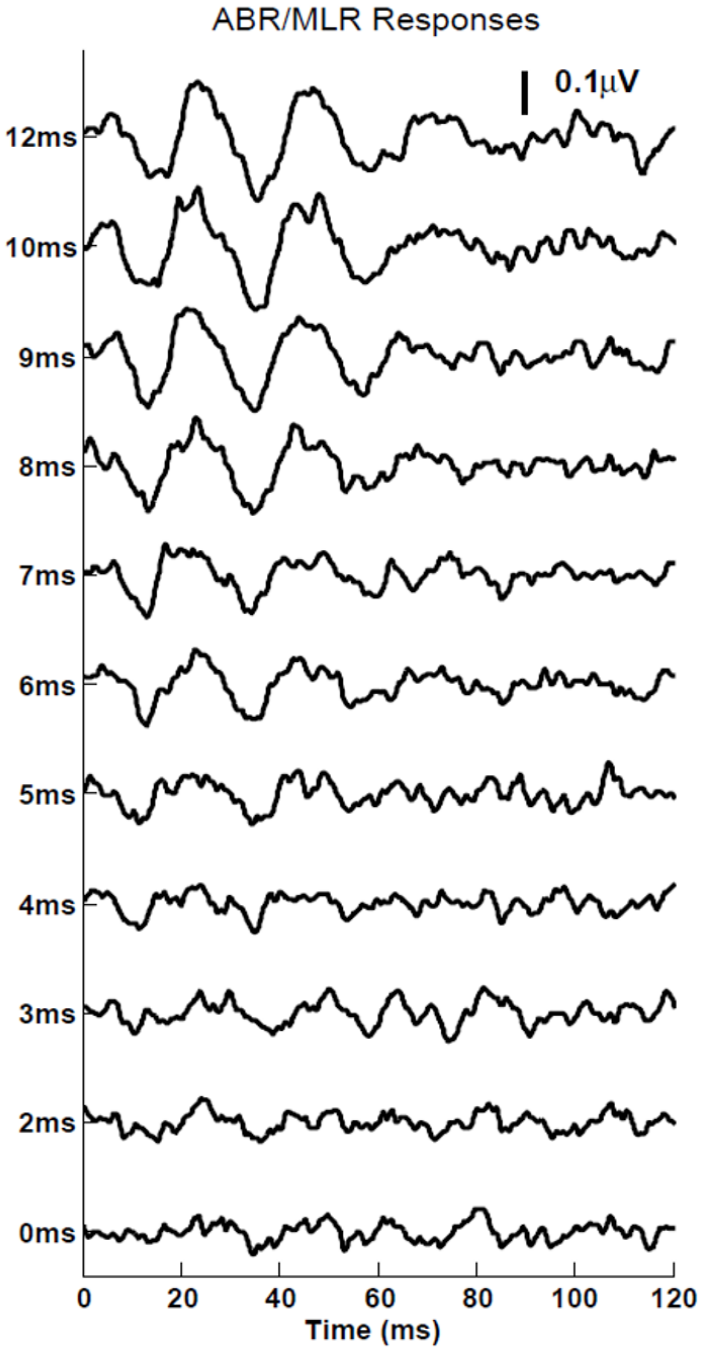


FIGURE 6.5. Grand population average of deconvolved responses to 40 Hz gaps. There are 11 traces for gaps between 0ms to 12ms gaps.

6.2.2 Objective Gap Detection Threshold (OGDT)

By using a 40Hz low jittered sequence, the resulting responses are convolved (QASSRs) with high magnitude corresponding to the stimulation rate. OGDTs were obtained by quantifying QASSRs responses using the Hotelling T2 test as described in Lachowska et al., (2012). A total of 2048 sweeps were averaged to get QASS responses for each gap duration (0ms -12ms gaps). Next, the fast Fourier transform (FFT) was used on each sweep to analyze the magnitude and phase of spectral beam corresponding to the stimulating frequency (f0). A non-null response was then detected by applying the T2 test to the array. Average phasors were plotted in addition to confidence ellipse (p=0.05) as illustrated in Figure 6.6 for subject S3. The response is significantly different from zero if the origin of the complex plane is outside the confidence ellipse.

As shown in the example of S3 in Figure 6.6, the longest gap elicited the largest signal. As the duration of the gap becomes shorter, the magnitude of the signal becomes smaller. The OGDT is assigned as the last duration in which the detection was significant. For the subject in Figure 6.6, the OGDT was 6ms because 5ms was not significantly different from zero. For all of the six subjects OGDTs were computed based on the Hotelling T2 test. OGDTs were shown in table 6.1 with maximum of 7ms and 5ms minimum OGDT with an average of 5.83ms.

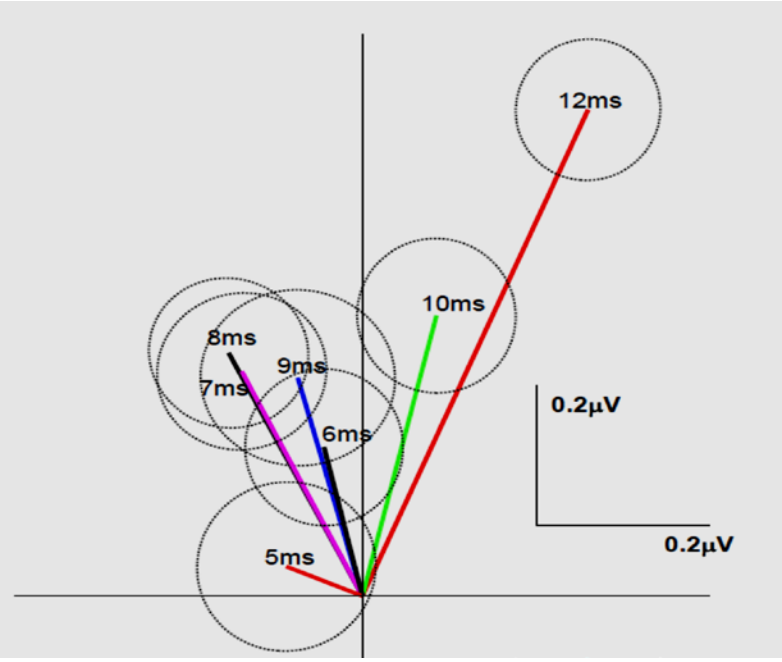


FIGURE 6.6. Example of OGDT for subject S3. Phasors and confidence ellipses of the fundamental stimulation frequency (f_0, 40Hz) spectral component of QASSRs elicited by gap in noise with durations ranging from 12ms to 5ms. Since the 5ms phasor's confidence ellipse (p=0.05) includes the origin of the complex plane, this response is not significantly different from zero; the OGDT is then 6ms.

TABLE 6.1 objective and behavioral gap detection thresholds

Subjects	OGDTs to 40Hz gaps(ms)	BGDTs ≥ 50% (ms)
S1	**5**	**5**
S2	**6**	**6**
S3	**6**	**7**
S4	**5**	**6**
S5	**7**	**6**
S6	**6**	**5**
Mean	**5.83**	**5.83**

6.2.3 Behavioral Gap Detection Thresholds (BGDT)

BGDTs were obtained from all six subjects with lowest BGDT equal to 5ms and highest equal to 7ms (mean of 5.83ms) as shown in Table 6.1. BGDT was calculated based on 3 or more successful attempts of gap detection out of six. Gap detection percentage as function of gap duration for all subjects is illustrated in Figure 6.7.

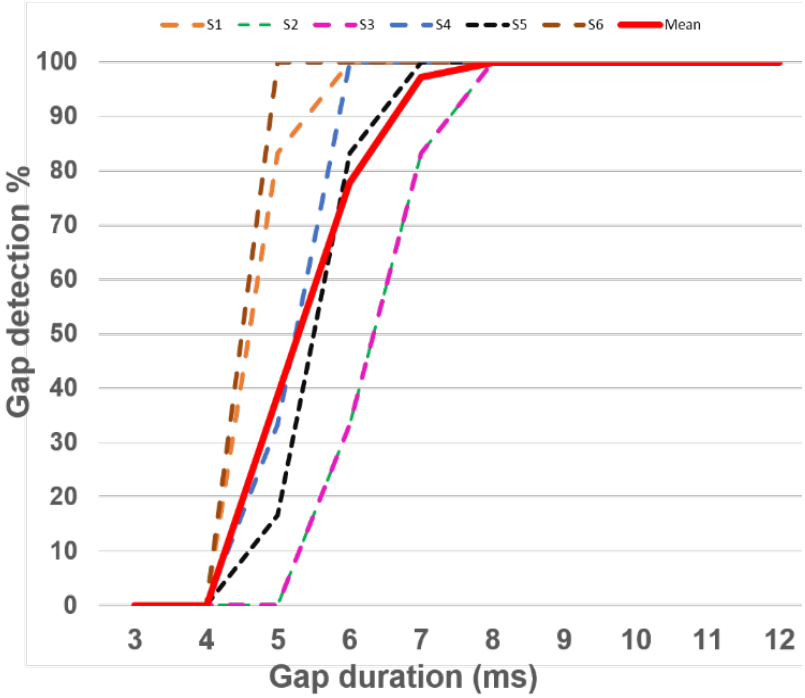


FIGURE 6.7. The mean gap detection percent illustrated as a function of gap duration.

6.3 Experiment III: Onset/Offset Effect on LLRs

In this experiment, 1Hz stimulation rate (one gap per second of noise) was used to evoke AEPs in eleven subjects. All responses were averaged around the onset of the noise as shown in figure 6.8. Each gap response is plotted with arrows pointing up and down; noise onset time location is represented by the arrow up while noise offset is represented by arrow pointing down as illustrated in figure 6.8 and figure 6.9. Responses evoked by different gap durations were different across both latency and amplitude. Because of the variations in latencies as gap duration changes (see figures 6.8, 6.9 and 6.10), the positive peak between 130 and 160 is tentatively labelled as the conventional P2 peak.

Moreover, the negative peak preceding the P2 will be named N1 and the negative peak after P2 is labelled as N2.

Grand averaged potentials of eleven subjects are shown in Figure 6.9. All noise onsets elicited a recognizable P2 and N2 peaks regardless of gap duration. In all responses, the P2 peak was the most prominent component across all gap responses. The largest amplitude of P2-N2 was observed for the 25ms gap duration. Additionally, the P2-N2 amplitude for gaps longer or shorter than 25ms was smaller as shown in Figure 6.10. The latency for P2 ranged between 137ms for the 300ms gap and 166ms for the 25ms gap as a result of the change in gap duration. Peak-to-peak amplitudes for the P2-N2 complex, and peak latencies in response to each gap duration are shown in the bar chart in Figure 6.10.

In all eleven subjects, the N1 wave was identifiable in response to 12ms, 25ms and 150ms gaps. However, in response to the 50ms gap, N1 was only identifiable in only nine subjects. For the 300ms gap, N1 was identifiable in eight subjects out of elven. N1 amplitude and latency were dramatically affected by gap duration as seen in the grand average responses Figure 6.8 for an individual subject (GAP010). The N1 response to the 300ms gap was small in contrast with the rest of the gap responses.

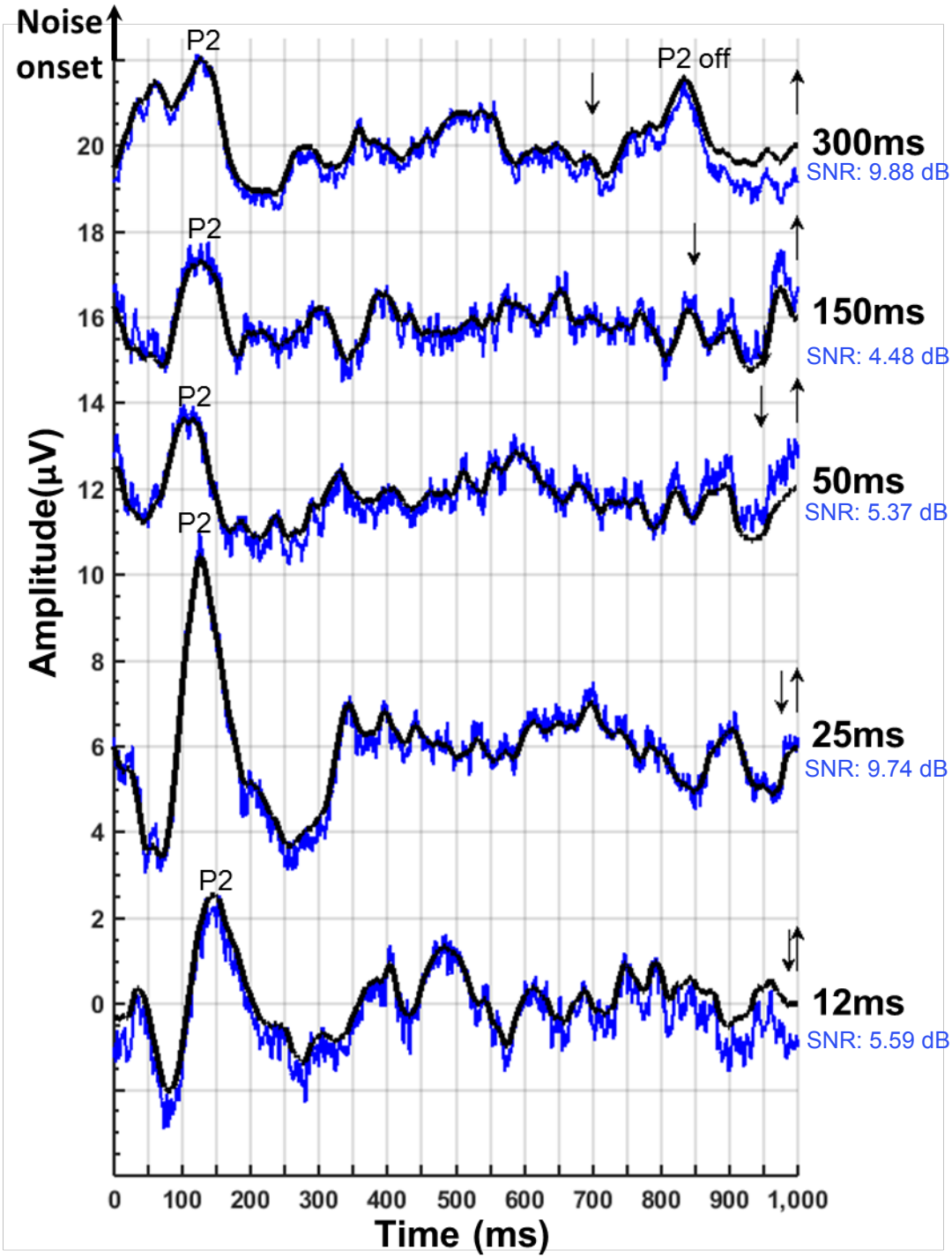


FIGURE 6.8. Responses from one subject (GAP010) averaged around noise onset for gap duration varied between 12ms and 300ms. The blue line is the signal with the original system filter settings (bandpass 1-1500Hz). The black line is the signal with post processing filter (bandpass 1-30Hz). Arrows are used to indicate the temporal location of noise onset (↑) and offset (↓).SNR for each gap duration trace is shown on the right.

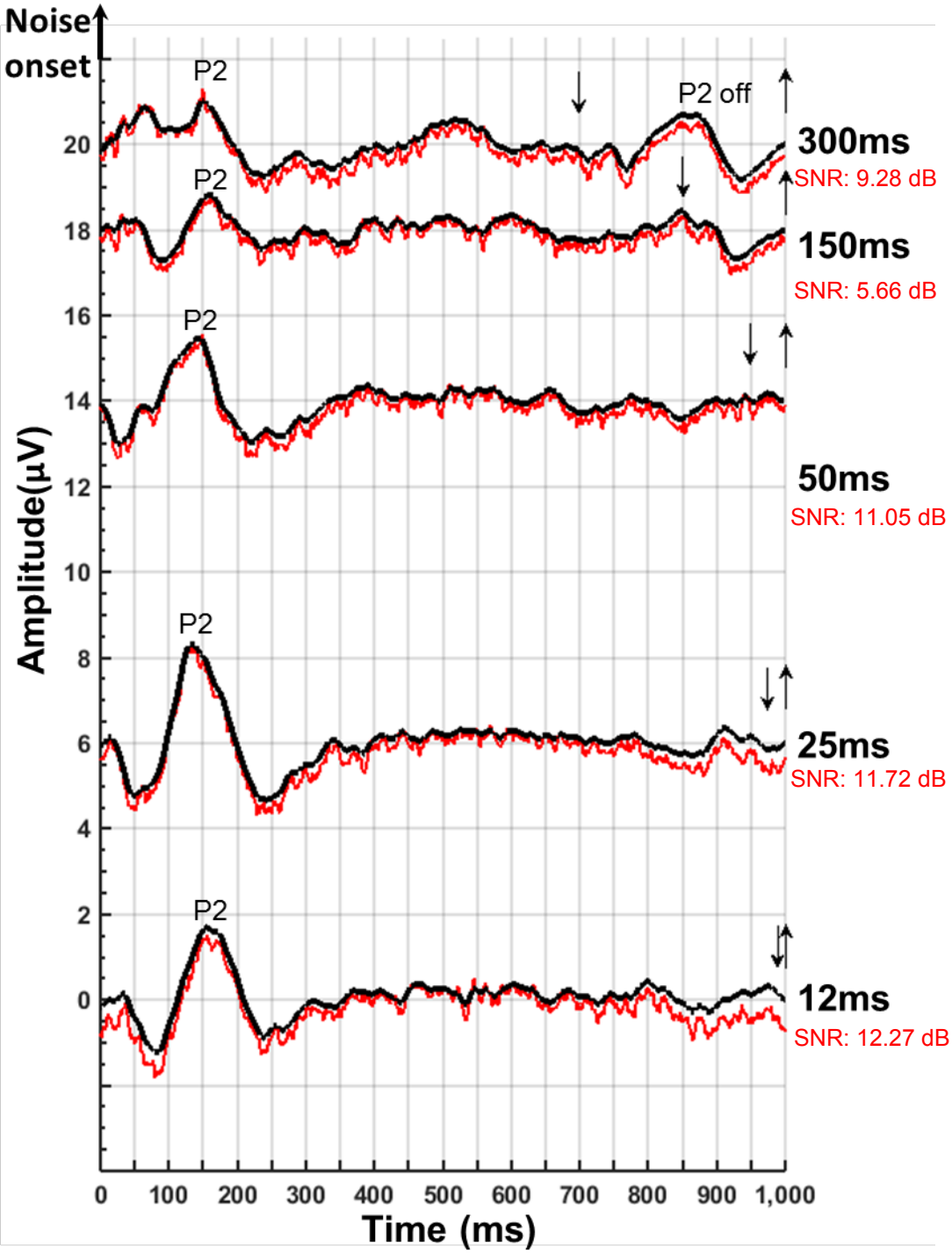


FIGURE 6.9. Grand average responses of eleven subjects, where t=0s corresponds to the noise onset for 5 gaps varied between 12 and 300ms. The red line is the signal with the original system filter settings (bandpass 1-1500Hz). The black line represents a bandpass of the data with a 1-30Hz.6dB/oct filter. Arrows are used to indicate the temporal location of noise onset (↑) and offset (↓). SNR for each gap duration trace is shown on the right.

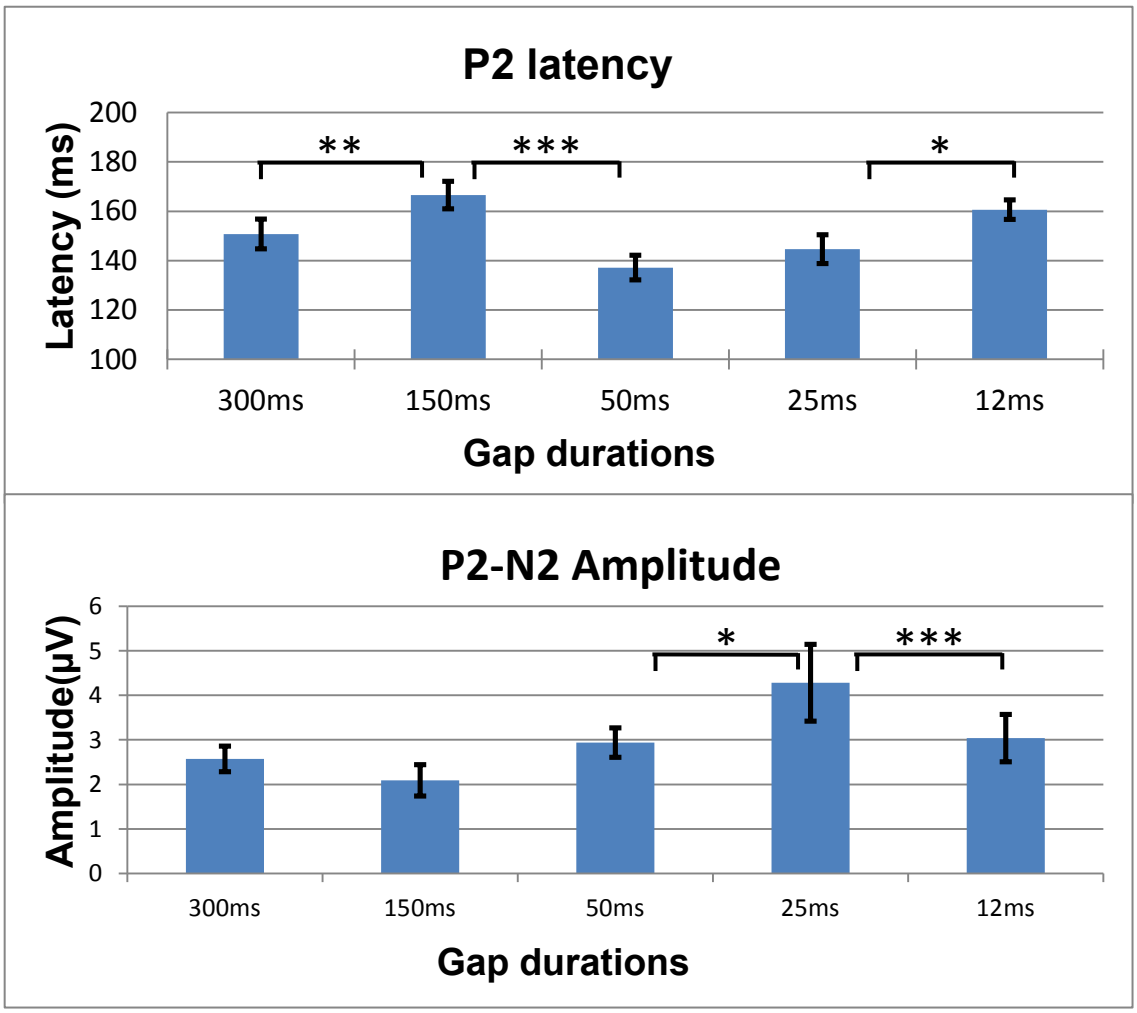


FIGURE 6.10. Mean amplitudes and latencies of the P2 peak for the eleven subjects in experiment III. The top bar chart shows the mean latencies with standard error bars. The bottom bar chart shows the mean amplitudes as a function of gap duration. Significance if present is marked as * $p<0.05$, **$p<0.01$, and *** $p<0.001$.

6.3.1 Offset Response

Responses to 300ms gap were characterized by two distinct responses; a response to noise onset and noise offset. The onset of the noise elicited a recognizable P2 and N2 components as described above. The onset and offset of the noise gap is indicated by arrows in figure 6.8 and 6.9 (down for offset)

Comparison between the noise onset and noise offset is shown in Figure 6.11. The mean P2-N2 complex amplitude for the onset response is 2.57μV while for the offset is 2.37μV. Onset and offset responses will be discussed in detail in experiment V.

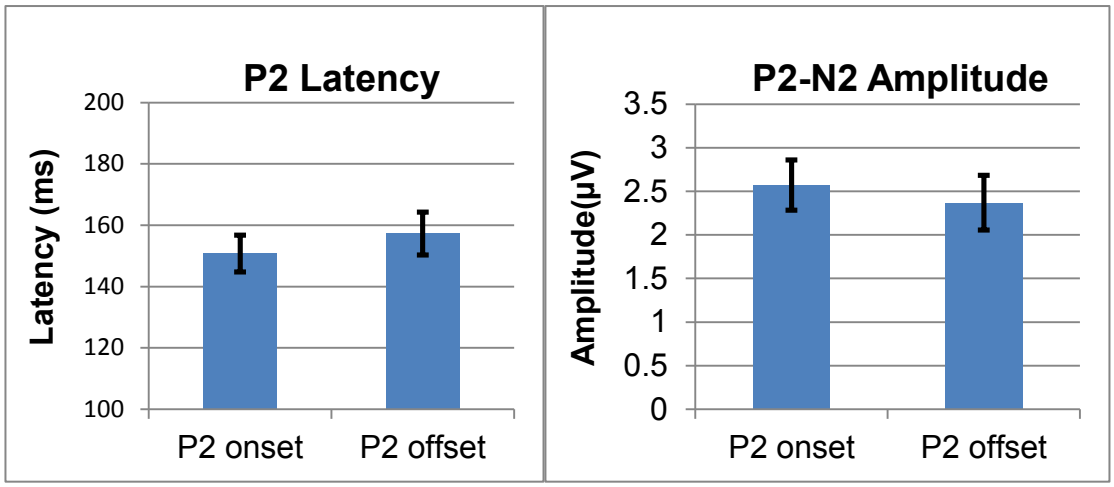


FIGURE 6.11. The P2 onset and offset response comparison for eleven subjects. The left bar chart shows the mean latencies with standard error bars. The right chart is for the mean P2 amplitudes of noise onset and offset.

6.4 Experiment IV: Onset/Offset Effect on LLRs (extended)

As discussed in the previous section, cortical responses to gaps were greatly affected by gap duration. As gap duration varies, changes in N1-P2 morphology were noticed. Therefore, we expanded the previous experiment by adding 5 gap durations. We aimed to precisely track the changes in AEPs by using 10 gap durations varied between 6ms and 300ms.

A total of seven subjects were recorded for this experiment while eleven subjects were recorded for experiment IV. However, the grand average

responses of 7subject were almost identical to the grand average responses of 11 subjects showed in experiment three for (300, 150, 50, 25 and 12ms) gap durations.

Similar to the previous experiment, the morphology of the N1-P2-N2 complex was clearly affected by gap durations. The gap duration effect is also seen in individual subject responses, as shown in Figure 6.12, as well as in the grand average responses of seven subjects in Figure 6.13. Responses to the longest tested gap durations (300ms or 250ms) showed two distinct responses. One response corresponds temporally to the noise onset and the other response to the noise offset. On the other hand, when the gap becomes shorter, one cortical response is seen.

Similar to experiment III, P2 was the most prominent peak despite the changes in latency or amplitude. Therefore, we focused mainly on changes of P2 amplitude and latency as the gap changes from 300ms to 6ms. To identify P2 in this study, we tentatively named the positive peak between 130 and 175 as P2. Additionally, P2 amplitude was calculated from the peak to the lowest negativity after P2. The mean latency and amplitude of P2 is shown in Figure 6.14.

For the individual (Figure 6.12) and population averaged responses (Figure 6.13), the largest P2-N2 amplitude is observed for the 25ms gap. The mean P2-N2 amplitude for 25ms gap is 4.45μV. Responses to gaps shorter than 25ms (12ms and 9ms) have smaller amplitude. Additionally, when the gap is 6ms, P2 becomes unrecognizable. On the other side, responses to gaps longer than 25ms are also smaller in amplitude. The smallest P2-N2 amplitude is

observed when the gap duration is 100ms (see Figure 6.13). For the 300ms gap, the onset and the offset of the noise produced two distinct responses, the mean P2-N2 amplitude is 2.71μV, which nearly half of the observed P2-N2 amplitude of the 25ms gap (4.45μV). P2 latency fluctuated between 135ms and 171ms as shown in Figure 6.14.

The negative peak preceding P2 is tentatively labelled as N1. The presence and the morphology of this N1 were also greatly affected by gap duration. Responses to 50, 25, 12 and 9ms gaps had an identifiable N1. However the shape of the N1 peak differs between gap responses as well as the latency. The mean latency of the N1 ranges between 71ms and 104ms. In response to 100ms gap, there is a positive peak that has a mean latency of 61.2ms. N1 appears in responses to gaps longer than 100ms (150, 200, 250 and 300ms). However, N1 amplitude in these responses is much smaller than for shorter gap responses as observed in the grand average responses in Figure 6.13.

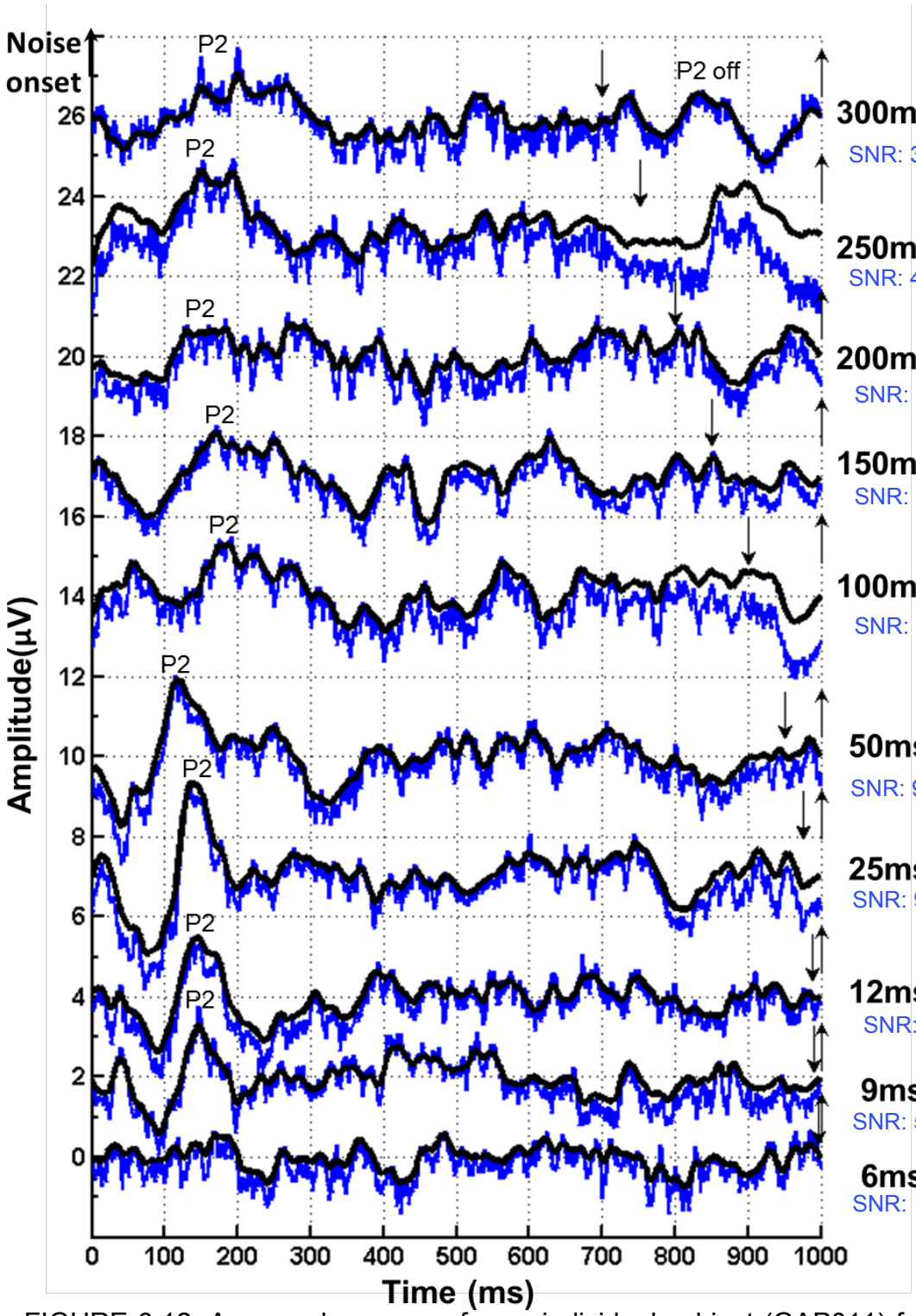


FIGURE 6.12. Averaged response for an individual subject (GAP011) for gap durations varied between 6ms and 300ms. The blue line is the signal with the original system filter settings (bandpass 1-1500Hz). The black line is the signal with post processing filter (bandpass 1-30Hz). Arrows are used to indicate the temporal location of noise onset (↑) and offset (↓).SNR for each gap duration trace is shown on the right.

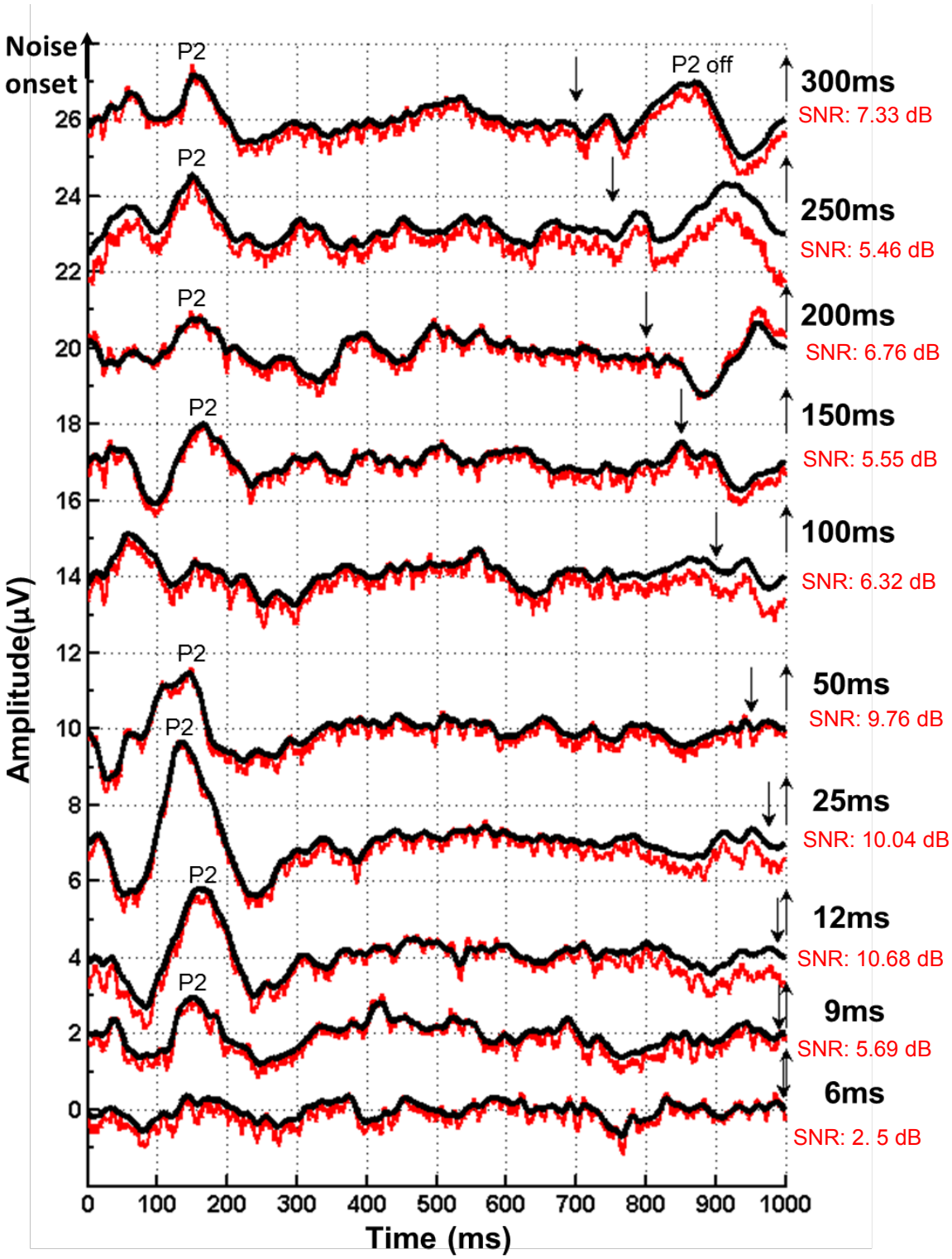


FIGURE 6.13. Grand average responses of seven subjects for 10 gap durations varied between 6 and 300ms. The red line is the signal with the original system filter settings (bandpass 1-1500Hz). The black line is the signal with post processing filter (bandpass 1-30Hz).). Arrows are used to indicate the temporal location of noise onset (↑) and offset (↓).

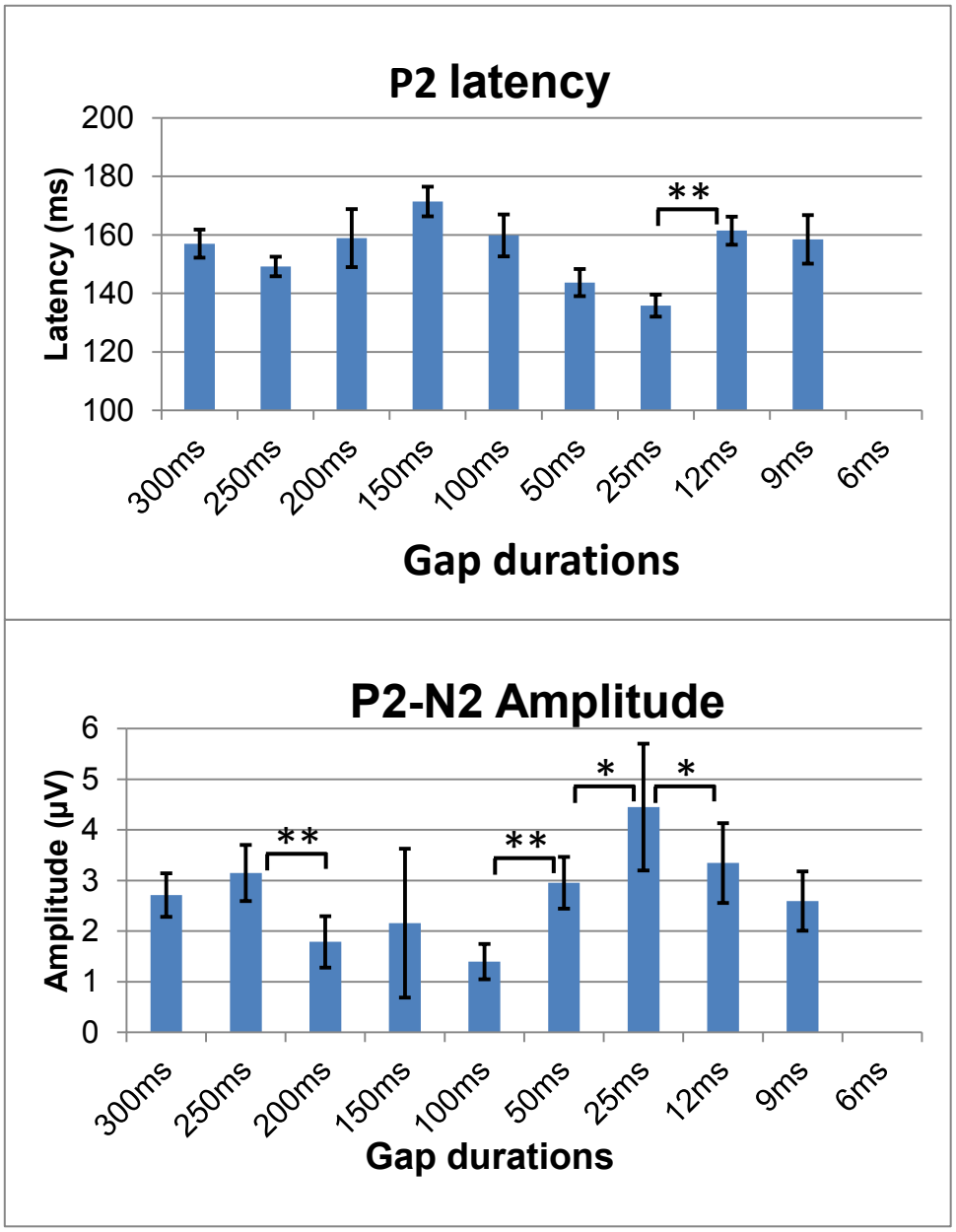


FIGURE 6.14. P2 mean amplitudes and latencies for seven subjects for 9 gap durations. The top bar chart shows the mean latencies with standard error bars. The bottom bar chart shows the mean amplitudes with standard error bars. Statistically significant differences between conditions is marked with * $p<0.05$ and ** $p<0.01$.

6.4.1 Offset Response

In experiment three, only 300ms gaps elicited two distinct responses; noise onset and noise offset response. In this experiment, 300ms, 250ms and 200ms gaps responses showed the noise offset response before it overlaps with the noise onset response. For these three responses, the offset response was characterized mainly By N1-P2 complex. Like the onset response, P2 was the most prominent peak in noise offset response.

P2 offset latency was measured from the offset of the noise as the noise offset location is changing with gap duration. In figure 6.15, P2 latencies are shown for three gap durations. Additionally, N1 offset latencies for 300ms, 250ms and 200ms gaps are between 88ms and 102ms. Finally, P1 offset was not clearly recognizable as a separate identifiable peak for the 200ms gap responses. However, it was identifiable in 300ms and 250ms gap responses as seen in figure 6.13.

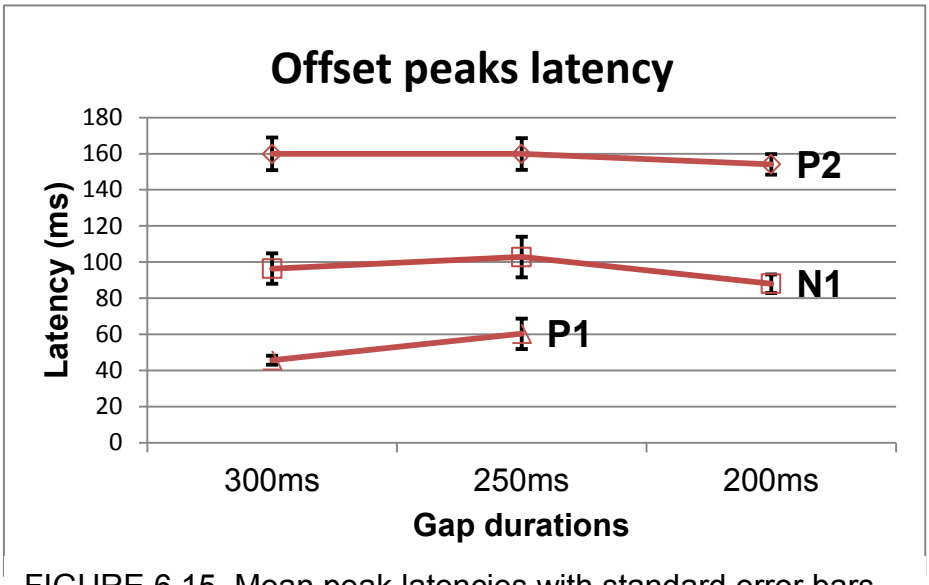


FIGURE 6.15. Mean peak latencies with standard error bars for offset responses. P1, N1 and P2 latencies are shown for three gap durations.

For consistency, the P2-N2 offset amplitude was calculated from P2 to the lowest negativity after P2. We were able to measure P2 amplitudes in both 300ms and 250ms responses. However, despite the existence of P2 in responses to 200ms gap, there was not enough time window for the negative peak to mature before the noise onset is presented again. Comparison of P2 between noise onset and offset of 300ms and 250ms gaps is illustrated in Figure 6.16. For the 300ms gap responses, the mean P2-N2 amplitudes for onset and offset are 2.71μV and 2.77μV, respectively. For the 250ms gap responses, the mean P2-N2 amplitudes for onset and offset are 3.15μV and 1.76μV, respectively.

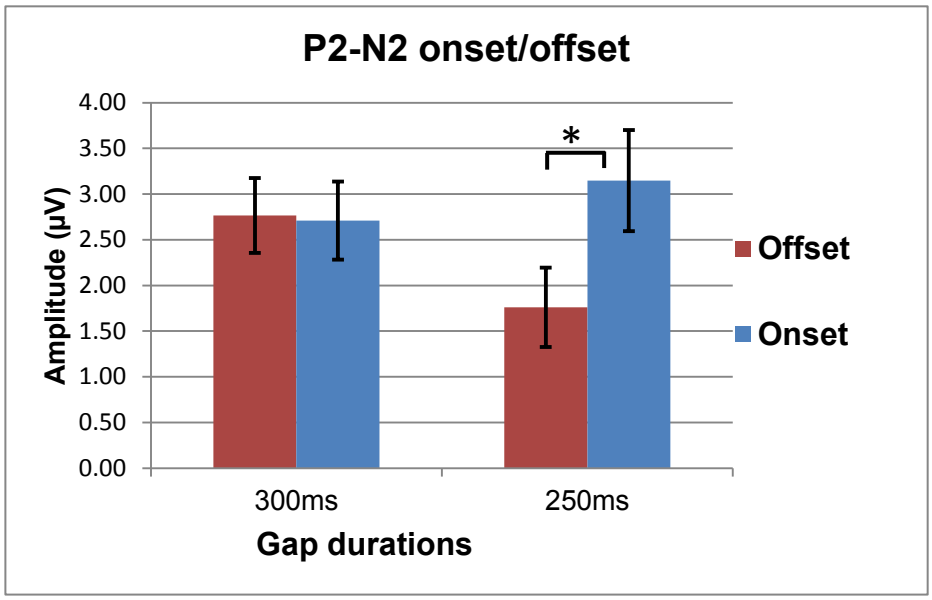


FIGURE 6.16. Amplitude comparison between onset and offset responses for the P2-N2 complex for the 300ms and 250ms gap responses. Significance, if present, is marked as * $p<0.05$.

6.5 Experiment V: Comparison between Double Clicks Reponses and Gap Responses

In experiment III and IV, the largest P2 amplitude was elicited using the 25ms gap. Additionally, the 300ms gap response has two distinct responses; onset and offset responses. Therefore, in this experiment we will compare between 25ms gap stimulus and two click stimuli separated by 25ms (double click). The 300ms gap responses are compared to two clicks separated by 300ms. The location of noise onset and offset is marked in Figure 6.17 and Figure 6.19 using up and down arrows to indicate onset and offset of the gap, respectively. The location of the click stimulus is marked using red vertical lines. The peaks evaluated in this experiment will include ABR, MLR, and LLR.

6.5.1 25ms Gap and Clicks

Responses for the 25ms condition (25ms gap and clicks separated by 25ms) are presented in Figure 6.17. All responses to 25ms double clicks and noise gaps exhibit the common late components N1, P2 and N2 of the CAEPs. Each of these peaks was, however, delayed and larger for the gap stimulus (see Figure 6.17). The P2-N2 amplitude was larger for the gap stimulus; with a mean of 4.45μV for gaps and 3.52 for double click, as shown in Figure 6.18. The mean P2 latency is 160ms from noise offset for the 25ms gap responses, while the P2 latency for double click is 18ms earlier (mean of 142ms) (see Figure 6.18). For the gap stimulus, a double peaked N1 was observed.

For double clicks early/middle components were well defined and appeared to correspond to conventional ABR/MLR components. For noise gaps, however, a more complex and broad positive waveform morphology was observed.

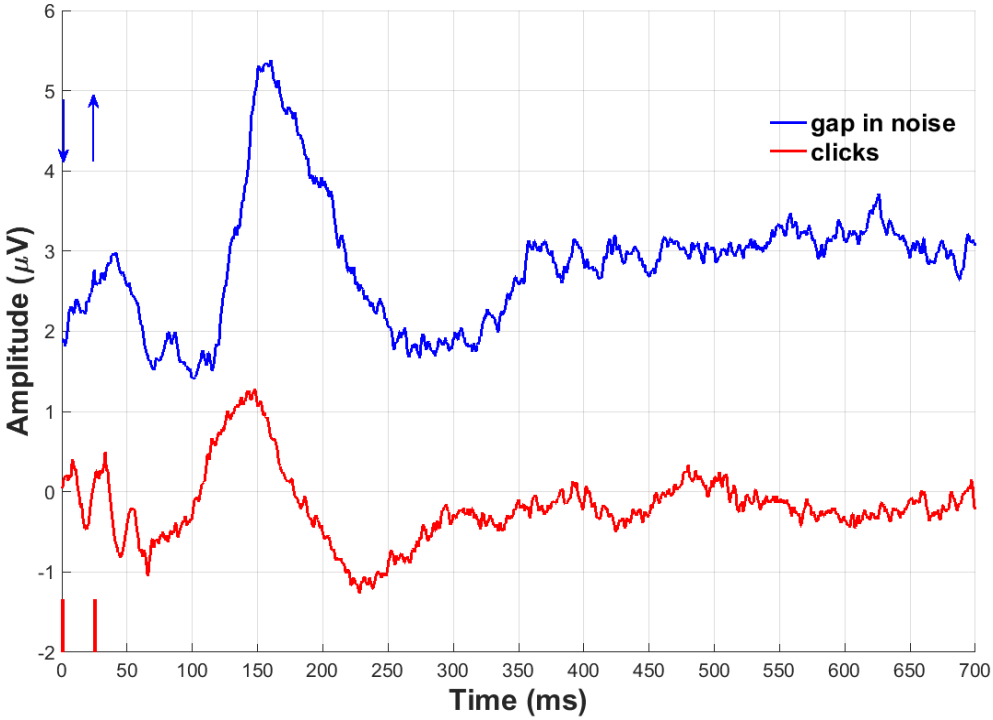


FIGURE 6.17. Grand average of 25ms doubles click (red) and 25ms noise gap in blue. Arrows are used to indicate the temporal location of noise onset (↑) and offset (↓).Vertical lines are used to indicate the locations of the first and second clicks.

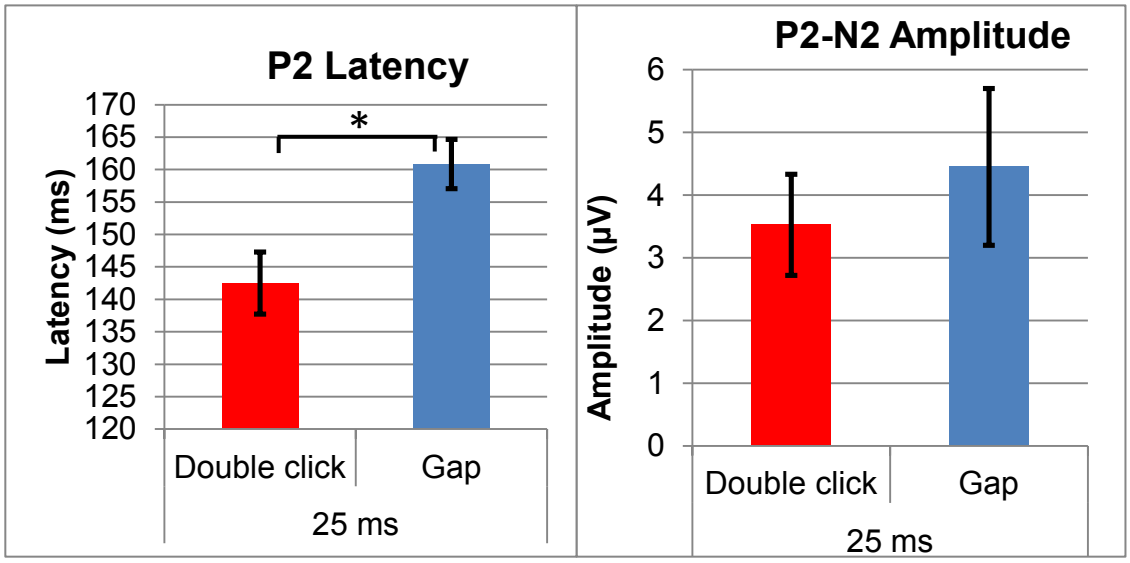


FIGURE 6.18. P2 mean amplitudes and latencies of seven subjects for 25 gaps (blue) and 25ms double clicks (red). The left bar chart shows the mean latencies with standard error bars. The right bar chart shows the mean amplitudes with standard error bars. Significance if present is marked as * $p<0.05$.

6.5.2 300ms Gap and Clicks

The clicks separated by a 300ms gap evoked fully formed AEPs (ABRs, MLRs and CAEPs) corresponding to each click. Figure 6.19 shows grand average responses for click (bottom) and noise stimuli (top). The P1 component, however, was not clearly observable in the second click. CAEP components (N1, P2 and N2) were fully formed in the response to the first and the second clicks. The duration of all stimuli in the current experiment is 1000ms, so the time window after the first click is 300ms, and the time window after the second click is 700ms.

Figure 6.20 shows the difference in morphology between the first and the second click responses. For ease of comparison of late responses, low-pass

filtered traces (black) are superimposed on the full bandwidth responses (color). P2 latency and amplitude did not show a significant difference between the first and second click responses (see Figure 6.22). For the first click, mean latency of the N2 peak is 214ms whereas latency in the second click is 218ms. Figure 6.23 shows a comparison between N2 onset and N2 offset mean latencies.

Responses to the 300ms gap-in-noise stimulus are characterized by two unique morphologies. The first response corresponds to the noise onset while the second response corresponds to the noise offset. Figure 6.19 shows grand average responses for the 300ms gap in noise stimulus, with the time of the noise onset and offset marked using up and down arrows, respectively. As shown in the figure, the time window after noise offset and before the noise onset is 300ms but the time window after the noise onset is 700ms.

A grand average response for the noise onset is characterized by early components (ABR/MLR) and late cortical components (the LLRs). The first notable positive peak in Figure 6.19 has a latency of 10ms, and is labeled as peak V; the second positive peak, Pa, has latency of 34ms. P1 in has a mean latency of 57.14ms in all seven subjects.

The cortical components N1, P2 and N2 were clearly identified in response to noise onset in all subjects. For the noise onset grand average response trace in Figure 6.19 and 6.20, the N1 peak has a mean latency of 112ms, and P2 has a latency of 150ms. The statistical mean of P2 latency for all seven subjects is

157.14ms as shown in Figure 6.22. Finally, N2 for noise onset has mean latency of 223ms.

Noise offset responses are shown in Figure 6.19 after the downward pointing arrow (↓), and the same response is zoomed for more clarity in Figure 6.20. As seen in the figures, responses to noise onset exhibit the typical ABR/MLR peaks, as well as late cortical peaks. However, a notable difference between noise onset and offset responses is in the first 50ms (ABR/MLR region). The ABR and MLR to noise offset had a dominant negative wave peaking at about 15ms. This negative wave is not observed to noise onset. Another dominant peak is P1 that has a latency of 50ms from noise offset. A comparison of P1 latency between onset and offset responses is shown in Figure 6.21. Statistical significance was observed for P1 latency between onset and offset conditions.

Furthermore, the offset response for both click and noise stimuli was characterized by dominant N1, P2, and N2 waves. However, latencies of the late component were different from noise offset latencies. N1 latency for the noise offset condition in the grand average is 71ms, whereas in the noise onset response has a mean latency of 112ms. In the grand average, P2 evoked during the offset has a latency of 173ms, while P2 for the onset has a latency of 150ms (see Figure 6.19 and 6.20). A comparison of P2 mean latency between onset and offset responses is shown in Figure 6.22. The N2 offset has a latency of 240ms, whereas N2 onset latency is 223ms. Figure 6.23 compares between N2 onset and N2 offset mean latencies.

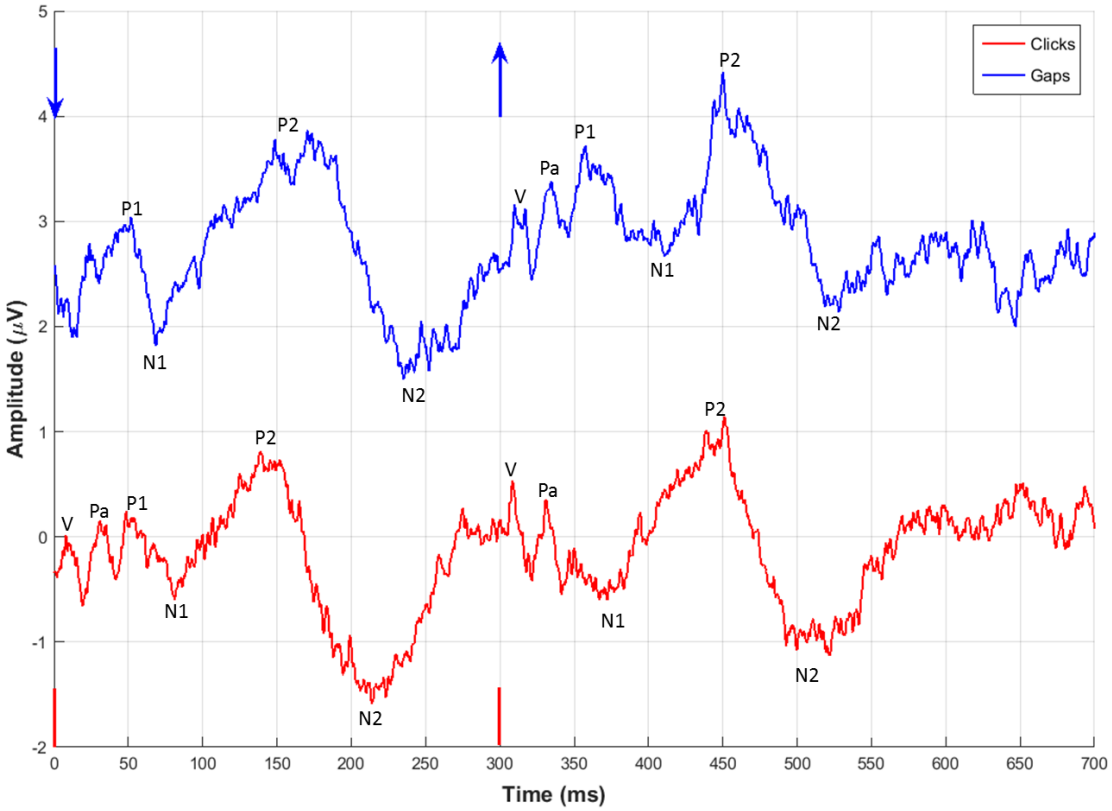


FIGURE 6.19. Grand average responses to 300ms click (red, bottom) and 300ms noise gap (blue, top). Arrows are used to indicate the temporal location of noise onset (↑) and offset (↓). Vertical lines at the bottom of the figure are used to indicate the locations of the first and second clicks.

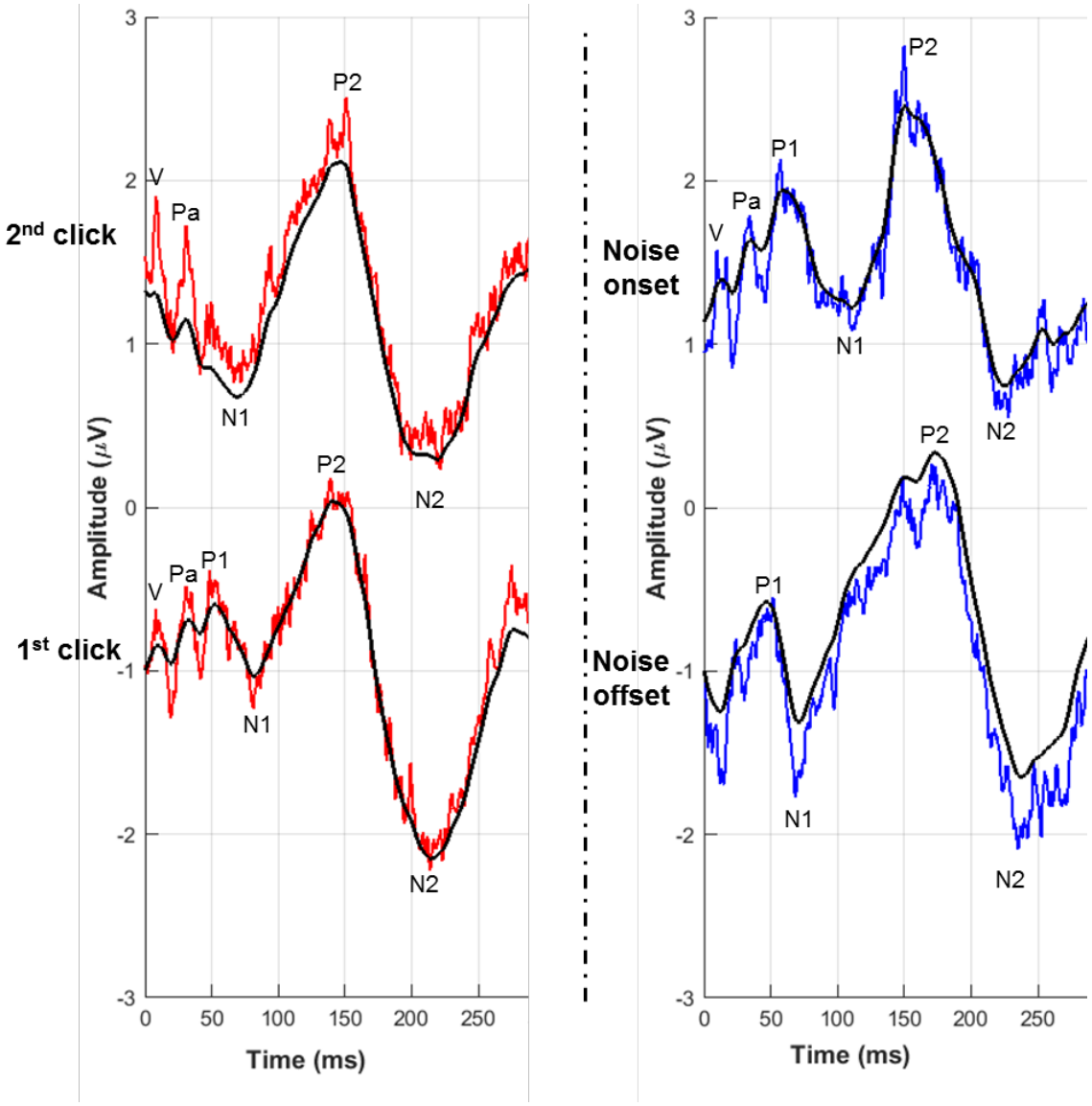


FIGURE 6.20. Grand averages for the 300ms doubles click (red) and 300ms noise gap (blue). Response is shown for the second click (left-top), the first click (left-bottom), and for the noise offset response (right-top), and noise onset response (right-bottom). The colored traces are the signals with the original acquisition filter settings (bandpass 1-1500Hz). The superimposed black traces are the same signals with a low-pass filter applied (bandpass 1-30Hz).

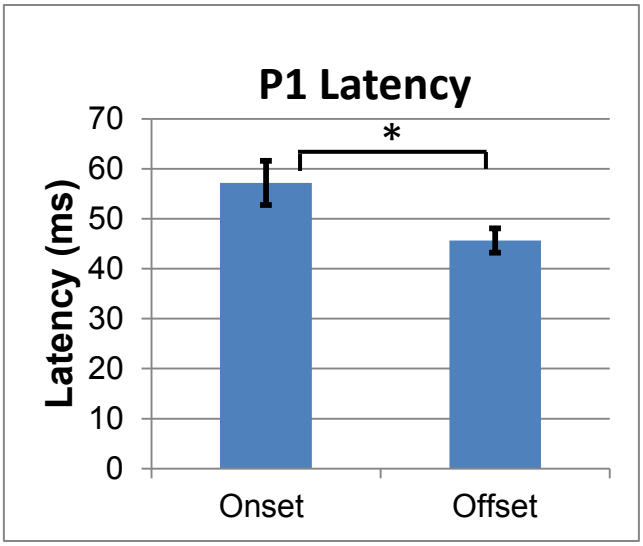


FIGURE 6.21. Mean P1 latencies with standard error bars for noise onset and offset responses. Statistical significance was observed for this condition ($p<0.05$).

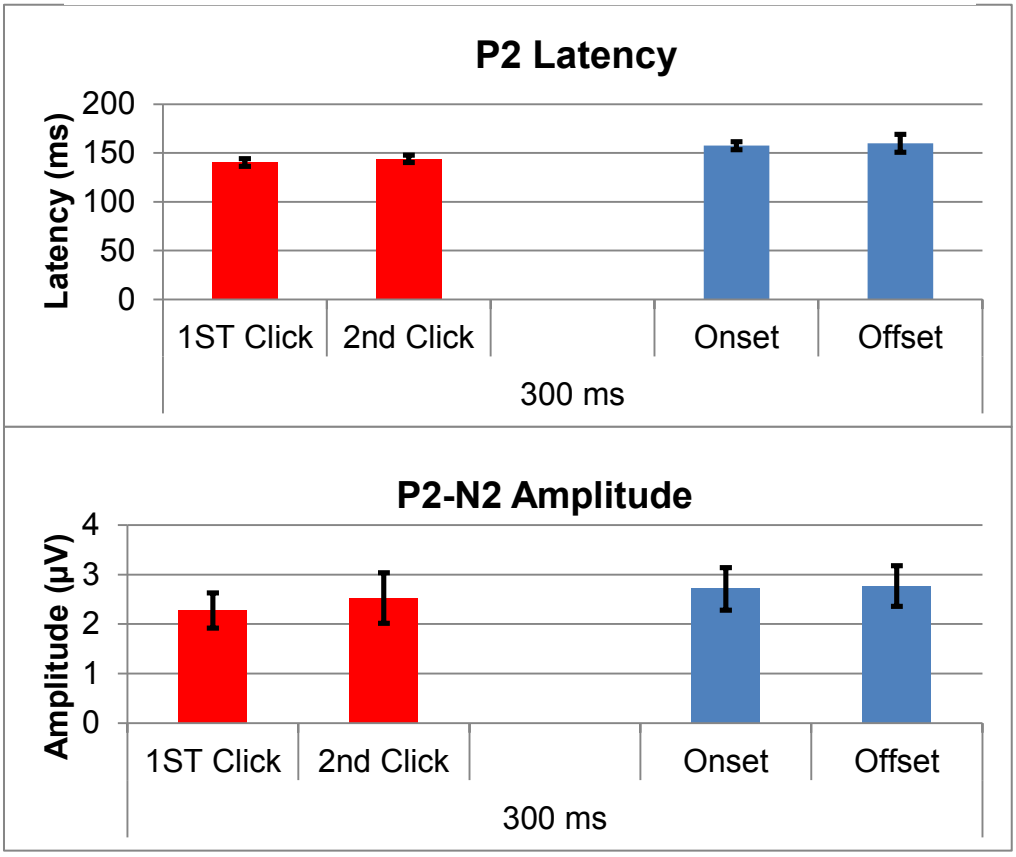


FIGURE 6.22. P2 mean amplitudes and latencies of seven subjects for 300ms gaps (blue) and 300ms double clicks (red). Top bar chart shows the mean latencies with standard error bars. Bottom bar chart shows the mean amplitudes with standard error bars.

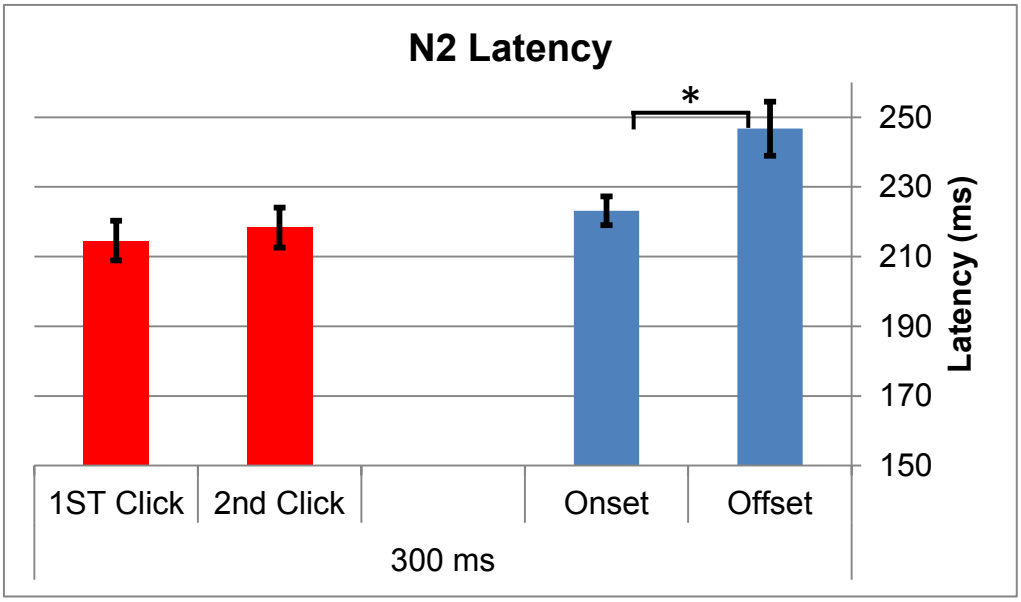


FIGURE 6.23. N2 mean latencies of seven subjects for 300ms gaps (blue) and 300ms double clicks (red). Bar chart shows the mean latencies with standard error bars. Latencies for N2 were statistically significant between onset and offset responses for the gap stimulus ($p<0.05$)

6.6 Experiment VI: Auditory Transient and Steady-State Evoked Potentials to Gaps in Noise

For the previous experiments, different gap durations were used to study gap MLRs, LLRs and ASSRs. For the current experiment, the effect of stimulation rate on AEPs is investigated by using only one gap duration (12ms), and varying the rate of presentation of the gap within the noise stimulus. A total of five stimulation sequences were utilized in this experiment, two at 40Hz, and one for 0.5, 1, and 5 Hz. As described in chapter five, experiment VI, two sequences were used to evoke 40Hz responses (see Figure 5.2 in chapter 5): a low jitter sequence for acquiring QASSRs, as well as an isochronic sequence to acquire conventional ASSRs. Then, by applying the CLAD deconvolution procedure to the QASSRs, the deconvolved transient ABR-MLRs were obtained.

Mean recording time and the number of sweeps differed between the 5 stimuli are given in Table 6.2. For each stimulus type, a sufficient number sweeps were averaged so that a high SNR (>10 dB) would be obtained for analysis. The number of sweeps was chosen to provide clear peaks and reduced background noise. The least recording time was obtained for the 40Hz SSR recordings (1677 sweeps, 6 min total recording time), and the longest was for 0.5Hz recordings (553 sweeps, 18 min).

TABLE 6.2 Mean number of sweeps averaged, SNR, and recording time for each of the stimuli type

Stimuli	Number of sweeps	SNR (dB)	Sweep length (sec)	Recording time (min)
0.5 Hz	553	10.47	2	18
1Hz	562	13.05	1	9
5Hz	3861	14.33	0.2048	13
40Hz QASSR	1926	12.64	0.2048	7
40Hz ASSR	1677	13.93	0.2048	6

In Figures 6.24, the 40Hz gap ASSR and QASSR are shown, as well as the deconvolved transient responses containing the ABR-MLR peaks. All the three responses were averaged around the noise offset as indicated by the arrows in top-left corner of Figure 6.24 (up indicating onset, down indicating offset). Comparison of 40Hz-gap ASSR and QASSR is performed in time domain (peak structure and amplitude) as well as in the frequency domain (magnitude and phase). Additionally, Figure.6.24 provides phasor analysis of ASSR and QASSR using the phase and magnitude of the fundamental stimulation rate in the frequency domain. QASSR measurements of magnitude and phase were very close to ASSR measurements.

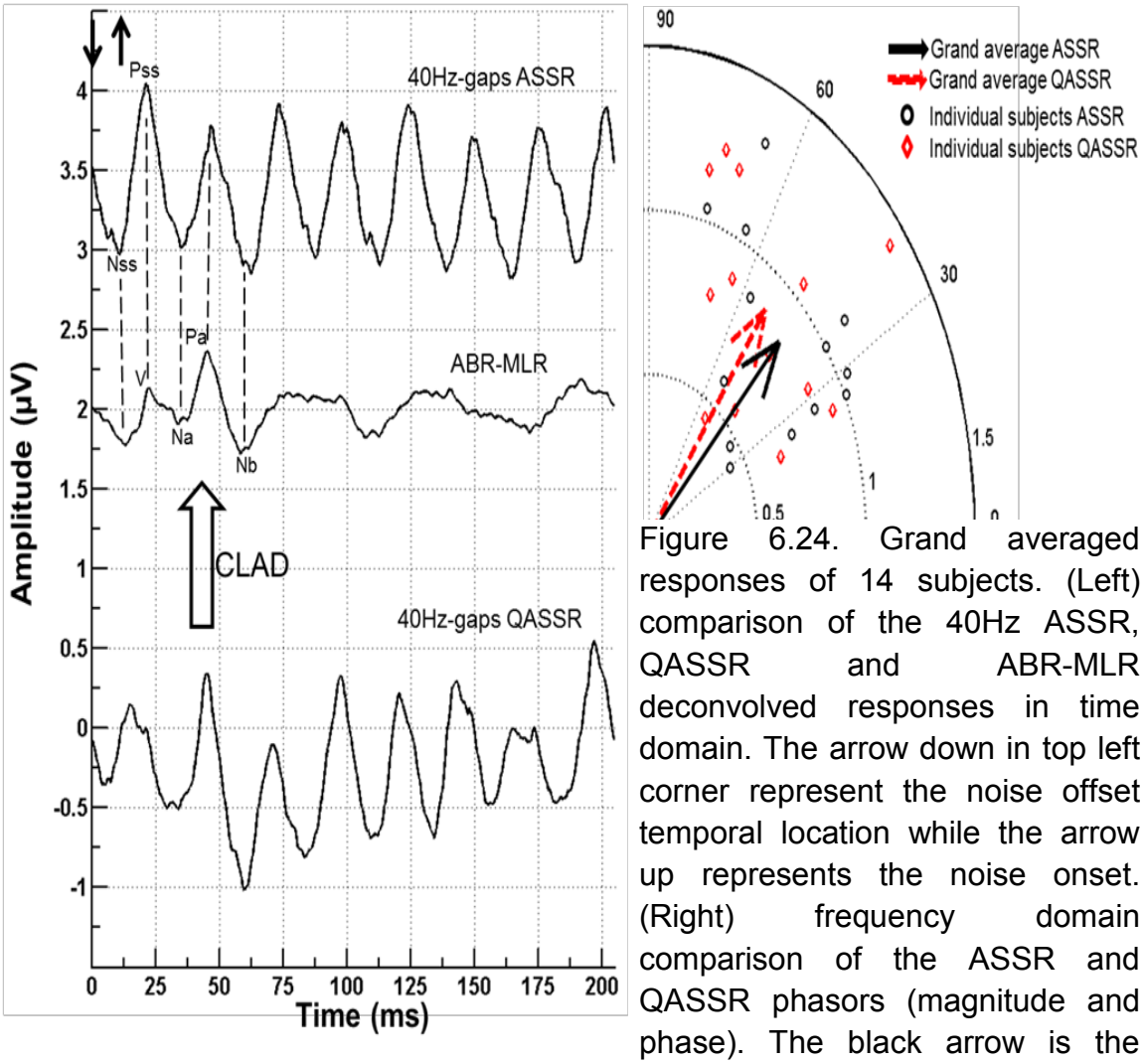


Figure 6.24. Grand averaged responses of 14 subjects. (Left) comparison of the 40Hz ASSR, QASSR and ABR-MLR deconvolved responses in time domain. The arrow down in top left corner represent the noise offset temporal location while the arrow up represents the noise onset. (Right) frequency domain comparison of the ASSR and QASSR phasors (magnitude and phase). The black arrow is the grand average of ASSR while black dots represent measurements from individual subjects. The QASSR are represented in red color.

Grand averages of all six stimulation conditions are shown in figure 6.25; from top to bottom: 0.5Hz, 1Hz, 5Hz, 40Hz (40Hz ASSR and 40Hz QASSR). All responses were averaged around the noise offset (gap onset). Latencies of all the detected peaks are shown in Figure 6.26 while the amplitudes of the prominent peak are presented in Figure 6.27.

For the 12ms gap presented at 0.5Hz, the response was mainly characterized by the presence of Pa, Pb, N1 and P2. However, Pb had a low amplitude and it was absent in 70% of the subjects. Table 6.3 provides a summary of the scored peak latencies for each peak and rate condition tested, as well as the number of subjects scored. Generally, N1 and P2 were the two most prominent peaks in the 0.5Hz responses. N1 latency from noise offset was 105ms (Std. Dev: 12) while P2 was 165ms (Std. Dev: 15). P1-N1 and N1-P2 amplitudes were 2.46μV (Std. Dev: 0.8) and 4.43 μV (Std. Dev: 1.33), respectively.

The 1Hz response had more pronounced ABR and MLR peaks compared to the 0.5Hz condition. As shown in Figure 6.25, 1Hz response was characterized by peak V, Na, Pa, Pb, N1 and P2 waves. Latencies for the 1Hz responses are shown in Figure 6.25. The mean amplitudes of the inter-peak intervals V-Na, Na-Pa, Pa-Nb, P1-N1, and N1-P2 are shown in Figure 6.27. The 1Hz response was the only response that showed all of the conventional ABR, MLR, and LLR peaks. Another important observation is that N2 was also observed at this rate. In the lower rate N2 component was not clearly observed.

The 5Hz and the deconvolved 40Hz responses both contained identifiable peaks V, Na, Pa, Pb peaks. The LLR peaks (N1 and P2) were not observed due to adaptation and the required averaging windows. The average peak latency for each wave is shown in Figure 6.26. Pa was the most prominent peak across all the four stimulation rates. As shown in Figure 6.26, 0.5Hz Pa latency is 49.2ms (Std. Dev: 5.4), 1Hz Pa latency is 47.7ms (Std. Dev: 3.4), 5Hz Pa latency is

47.0ms (Std. Dev: 1.4), and 40Hz Pa latency is 44.7ms (Std. Dev: 1.4). Finally, 40Hz gap ASSR is characterized by eight peaks that correspond to the stimulation rate as shown in Figure 6.24 and 6.25. The first three peaks of the ASSR and QASSR closely corresponded to the wave V, Pa and Pb peaks.

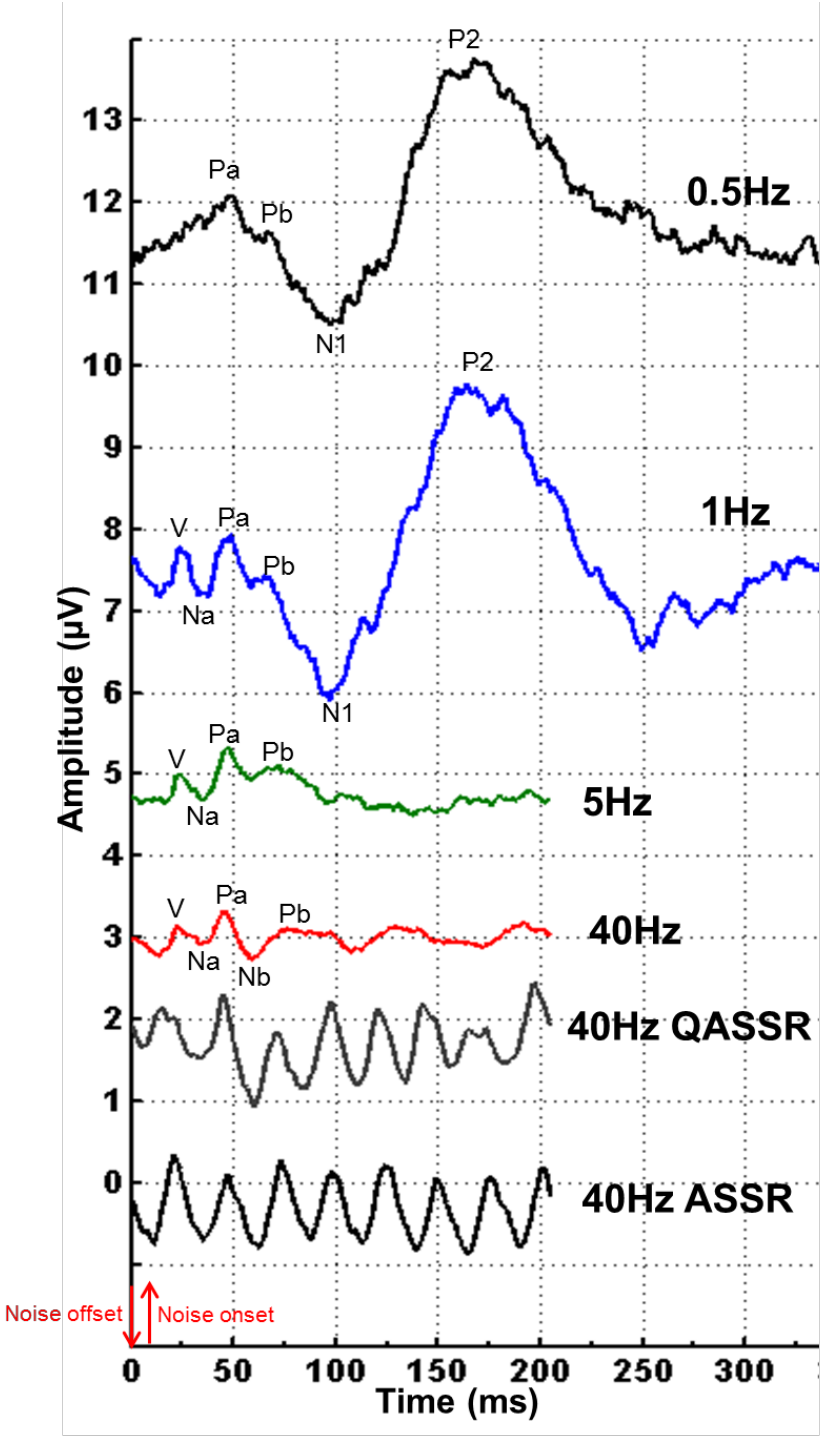


Fig. 6.25. Grand averaged transient responses (14 subjects) for all four stimulation rates arranged in decreasing order (0.5Hz, 1Hz, 5Hz, and deconvolved 40Hz). 40Hz QASSR and 40Hz ASSR traces are at the bottom. Major peaks are labelled as identified in each trace.

TABLE 6.3. Mean latencies (first row) and standard deviations (second row) of the 7 major peaks identified at 4 rates in 14 subjects. Peak identification percentages are indicated in the third row of each bow. No latency is given when identification percentage is below 60%.

Rates	V	Na	Pa	Nb	Pb	N1	P2
0.5 (Hz)	-	-	**49.2**	-	-	**105.0**	**165.1**
	-	-	*(5.5)*	-	-	*(12.3)*	*(15.1)*
	29%	36%	100%	21%	29%	100%	100%
1 (Hz)	**25.0**	**35.4**	**47.7**	**57.2**	**66.3**	**101.0**	**170.8**
	(1.9)	*(2.8)*	*(3.4)*	*(2.6)*	*(4.0)*	*(8.9)*	*(12.8)*
	93%	100%	100%	93%	93%	100%	100%
5 (Hz)	**24.1**	**35.8**	**47.0**	**58.3**	**71.3**	-	-
	(1.6)	(2.2)	(1.5)	(3.7)	(6.5)	-	-
	100%	93%	100%	93%	93%	0%	0%
40 (Hz)	**22.8**	**36.5**	**44.8**	**59.6**	**74.0**	-	-
	(1.1)	*(2.1)*	*(1.4)*	*(5.1)*	*(5.3)*	-	-
	78%	72%	100%	100%	78%	0%	0%

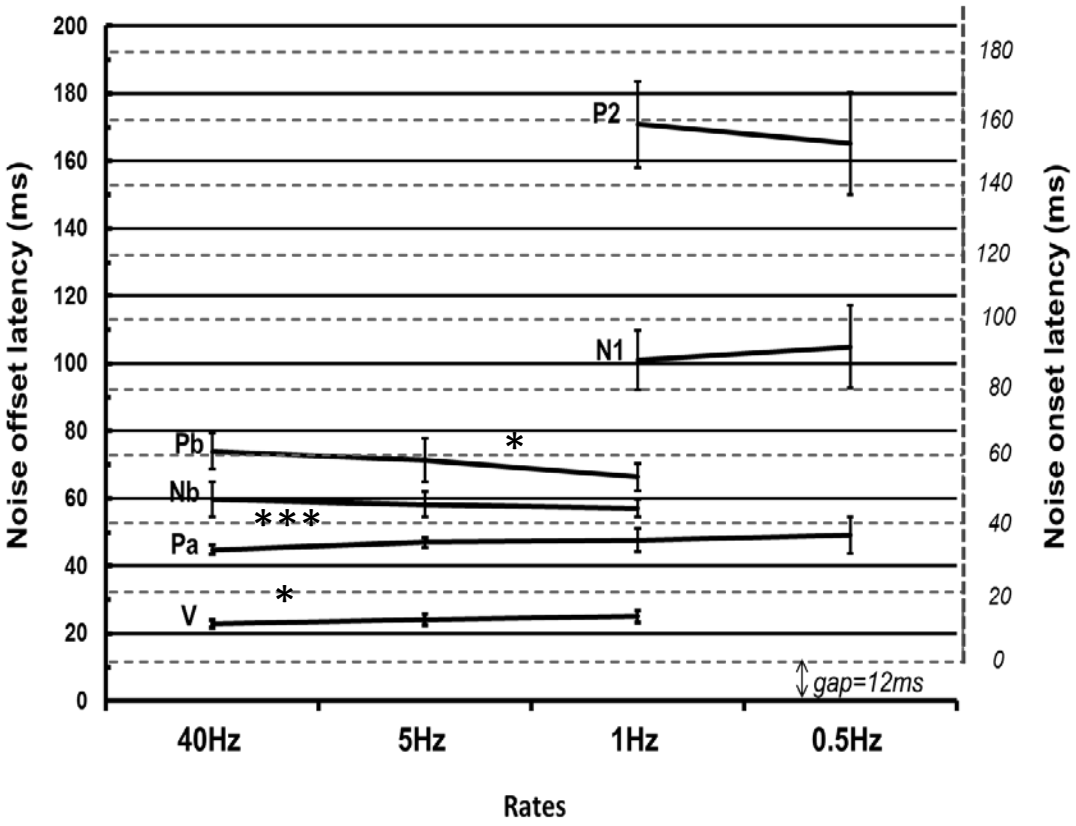


FIGURE. 6.26 Mean latencies and standard deviations of the detected AEP peaks (wave V through P2) plotted as a function of noise offset (left axis, solid lines) and noise onset (right axis, dashed lines). The right vertical axis is shifted by 12ms gap duration as indicated at the bottom right. Significance if present is marked as * $p<0.05$, ** $p<0.01$, and *** $p<0.001$.

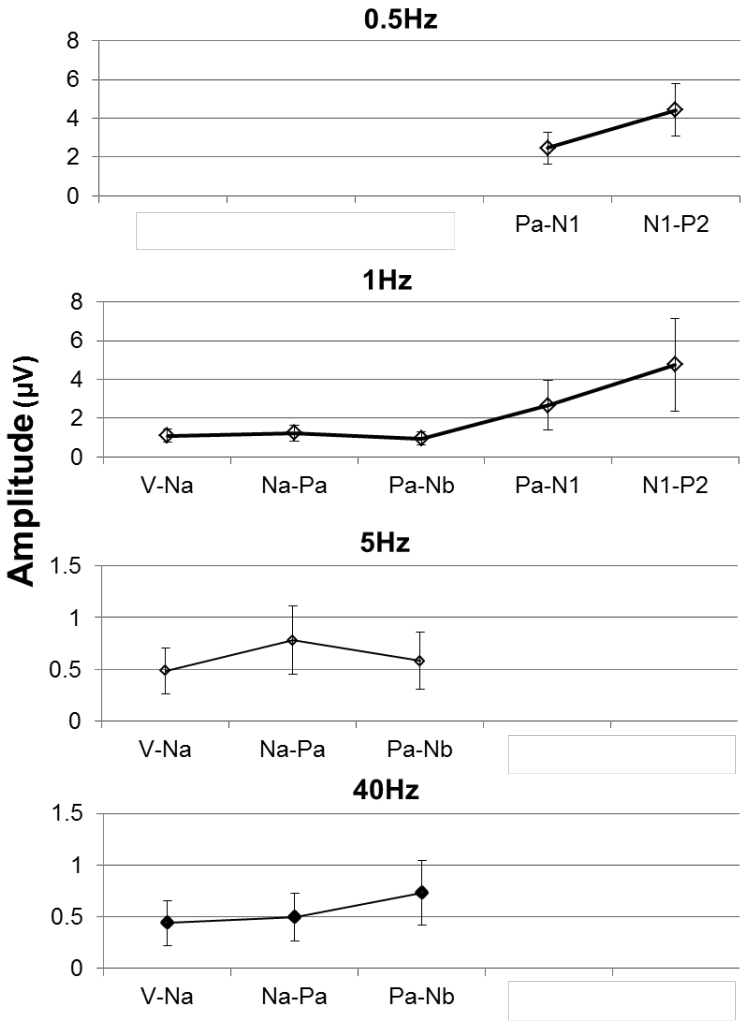


FIGURE 6.27. Mean amplitudes and standard deviations of the transient responses from the four rates plotted separately. Five inter-peak amplitude measurements (V-Na, Na-Pa, Pa-Na, Pa-N1 and N1-P2) are used.

CHAPTER 7: DISCUSSION AND CONCLUSION

Poor temporal resolution has been linked to complications in speech perception (Gordon-Salant & Fitzgibbons, 1993), and has been shown to be associated with syndromes such as autism, auditory neuropathy, multiple sclerosis (Bhatara et al., 2013; Eggermont, 2015; Michalewski et al., 2005; Musiek et al., 2005; Rabelo et al., 2015) as well as aging (Harris et al., 2012; Harris et al., 2010; Palmer and Musiek, 2014). Therefore; behavioral gap noise tests have been widely explored in order to evaluate the temporal resolution. Various behavioral gap detection tests have been shown to be sensitive tool for temporal resolution assessment (Musiek et al., 2005).

However, temporal resolution cannot be evaluated effectively using current psychophysical testing paradigms in some populations (e.g. Infants, young children or any uncooperative individual). Several researchers have investigated the use cortical gap in noise responses as an alternative method. Furthermore, AEPs evoked by gaps in noise may provide insights of how AEPs morphology and latency differ from AEPs evoked by conventional stimuli (e.g. clicks or tones). Additionally, by comparing behavioral gap thresholds and AEPs may explain the elevation of the gap detection thresholds in some populations. Also, it may provide insight into the mechanisms of the gap processing and temporal perception in the brain.

In general, most research for gap stimuli have looked at cortical gaps responses presented at 0.5 Hz or slower using gaps of 20ms duration and shorter (Harris et al., 2012; Michalewski et al., 2005; Palmer and Musiek, 2013). Two studies investigated gap-evoked ABR as an objective measure for temporal resolution (Poth et al., 2001; Werner et al., (2001). No reachable study has investigated MLR or ASSR to gaps in broadband noise. Additionally, the effect of presentation rate on AEP components was not fully investigated.

However, there was a need for more research on the use of gaps AEPs in order to determine an optimal method to evaluate auditory temporal resolution objectively. The aim of this dissertation was to study ABRs, MLRs, LLRs and ASSRs elicited by gaps in broadband noise. Additionally, we explored the effect of stimulation rate (gaps per second) and gap duration on the morphology of auditory responses. An objective method to obtain gap detection thresholds using gaps presented at 40Hz was presented. Finally, the difference between gap offset and gap onset responses was investigated. In the following sections, the effects of gap duration on early and cortical responses are compared using our findings with other published findings. Then, the rate effect on gap responses is discussed. Finally, results of the noise onset and offset responses are discussed. The experiments and findings presented in this dissertation contribute to a better understanding of the effects of: a) gap duration, b) stimulation rate and c) noise offset response, and will provide more insight of the electrophysiological assessments of temporal resolution and its neural processes.

7.1 Gap Duration

Exploring the effects of gap duration on the auditory electrophysiological recordings was one of the aims in this dissertation. The scope of the investigation includes not only the cortical responses but also ABRs, MLRs and ASSRs. In all the presented experiments, short and long gaps were utilized to evoke AEPs. For clarity, gap durations were separated into a) short gaps (25ms and shorter); b) medium gaps (50, 100, 200ms); c) long gaps (250 and 300ms).

In experiment II, short gaps varying between 0ms (no gap) to 12ms were used to record 40Hz ABR-MLR and 40Hz QASSRs. In the other experiments, the duration of the gaps varied between 6ms and 300ms. In summary, the effect of gap duration on AEPs was studied by analyzing the latency, amplitude and morphology of the waves.

7.1.1 Cortical Responses

Several studies on gap-evoked cortical responses have shown that N1-P2 amplitude diminishes with shorter gaps (Harris et al., 2012; Michalewski et al., 2005; Palmer and Musiek, 2013; Pratt et al., 2005). 15ms gap was the largest gap duration in Harris et al (2012). They found that 15ms gap responses evoked the largest N1-P2 amplitude and it diminishes as the gap gets smaller. Similar duration effects were observed by Michalewski et al. (2005) and Pratt et al (2005) in response to 20ms (and shorter) gaps.

In Palmer and Musiek (2013), three gap durations were chosen based on the BGDTs. The three gaps were as follows: suprathreshold gap (20ms); near-threshold gap (BGDT+2ms); and subthreshold gap (2ms). They showed that N1-

P2 amplitude in 20ms gap responses was larger than BGDT+2ms responses and absent in 2ms responses.

For short gaps (less than 20ms), it was observed that N1-P2 decreased in amplitude as gap decreased regardless of the stimulus design specifications (sound intensity, stimulation rate, gap envelope design) (Harris et al., 2012; Michalewski et al., 2005; Palmer and Musiek, 2013; Pratt et al., 2005). Our results of cortical responses presented in experiment III and IV were in agreement with the other studies mentioned above for short gaps. The 25ms gap evoked the largest N1-P2 amplitude as shown in Figure 6.13 and 6.14. However, the results presented in section.6.4 found that N1-P2 becomes smaller for medium and long gaps. As shown in the results (Figure 6.13), responses of medium gaps become smaller until we start observing two distinct responses (onset and offset) for long gaps.

In regards to gap duration and latencies, the N1 and P2 latencies were altered by gap duration in some studies but absent in others. Some studies have shown no significant effect of gap duration on N1 and P2 for short gaps (less than 20ms) (Harris et al., 2012; Palmer and Musiek, 2013). In contrast, Michalewski et al. (2005) and Pratt et al. (2005) found that wave latencies were significantly affected by gap duration. Specifically, they reported that N1 and P2 latencies increased significantly as the gap duration increased.

The effect of gap duration on wave latencies and morphology was clearly observed in the results presented above (see Figure 6.13). The 25ms gap responses showed a significantly earlier N1 and P2 than 12ms and 9ms

responses. No significant change in P2 latency between 12ms and 9ms responses was observed. The results presented above suggest that latencies at the cortical response peaks are dependent on the onset and offset of the gap.

For long gaps (250 and 300ms) responses, two distinct responses were observed corresponding to the noise onset and offset. As the duration between noise onset and offset (which is the gap duration) becomes shorter, the onset and offset responses become superimposed. For the 200ms, 150ms and 100ms gaps, noise onset responses showed diminished P2-N2 amplitude compared to the 300ms and 250ms. The morphological changes observed are caused mostly by a destructive interaction between the noise onset and offset responses for the medium gap durations (200,150 and 100ms).

As seen in Figure 7.1, for the 100ms gap responses, the P2 peak results from the addition (superposition) of P1 on and P2 off responses. P2 off and N2 off responses destructivity added. By contrast, in the 50ms gap response, the interaction starts to be constructive as the P2-N2 amplitude start increasing. For 25ms gaps, the interaction appears to be mostly constructive. For short gaps (less than 25ms), the author hypothesizes that the amplitude starts decreasing mainly due to the adaption and masking effects not the destructive interference between the onset and the offset.

For, among all gap durations tested, the 25ms gap elicited the largest amplitude P2-N2 response in all subjects. Some of the possible explanations for this enhanced P2-N2 amplitude is that the effect of response adaptation between noise onset and offset is minimal compared to shorter gaps (12ms and 9ms), or

that the constructive interference of noise onset and offset is highly effective at 25ms gap, or a combination of these two.

For the 25ms gap responses, the grand average P2-N2 amplitude was 4.5μV, which is about 75% larger than the 300ms onset (P2-N2: 2.7μV) or offset (P2-N2: 2.8μV) response. Therefore, we grossly hypothesize that the interaction between noise onset and offset is mostly constructive for the 25ms gap. To test this hypothesis of the role of noise onset and offset interference in the morphological changes of gap responses we did a gap simulation analysis.

Gap Simulation Analysis

In this section, we tested the hypothesis of the contribution of noise onset and noise offset in gap responses. Gap responses were simulated by adding the independent onset and offset responses. Then the simulated gap responses were compared to the recorded gap responses. The question was whether the simulated gap responses will be similar to the recorded gap responses.

The onset and the offset responses were decomposed from the 300ms gap responses (300ms gap and 700ms noise segments repeated in serial). The onset and the offset responses were then used to generate synthetic gap responses for 10 gap durations'. In theory, if simple superposition is responsible for the morphology of the recorded responses, it would be possible to generate synthetic gap responses for gaps shorter than 300ms by adding the onset and offset responses. As observed in Figure 6.13, the AEP responses are almost flat after 300ms. This is expected since no cognitive processing (e.g. 300 waves) is ongoing requiring attention. If this assumption is valid, then the summation of the

onset and the offset responses would be similar to the recorded gap responses to great extent.

The following gap response durations were synthesized: 250, 200, 150, 100, 50, 25, 12, 9, and 6ms, using the filtered (1-30Hz) 300ms gap response. Figure 7.1 illustrates the simulation of a 100ms gap response. First, we decomposed the noise onset segment (700ms) and noise offset (gap onset) segment (300ms) (see Figure 7.1). Second, we shifted the noise offset response by a the corresponding gap duration (e.g. 100ms). Finally we add the two responses (onset and offset) to synthesize gap responses (simulated gap responses).

Recorded and simulated gap responses are shown in Figure 7.2, as well as the constituent onset and offset waveforms, shifted accordingly (red and blue). Each subplot in the figure shows the recorded gap response as well as the simulated gap response. As shown, the simulated gap responses for durations of 50, 100, 150, 200, and 250ms (black traces) were very similar to the recorded gap responses (green traces). For gaps below 25ms, the recoded responses are diminishing in amplitude while the simulated gap responses are increasing.

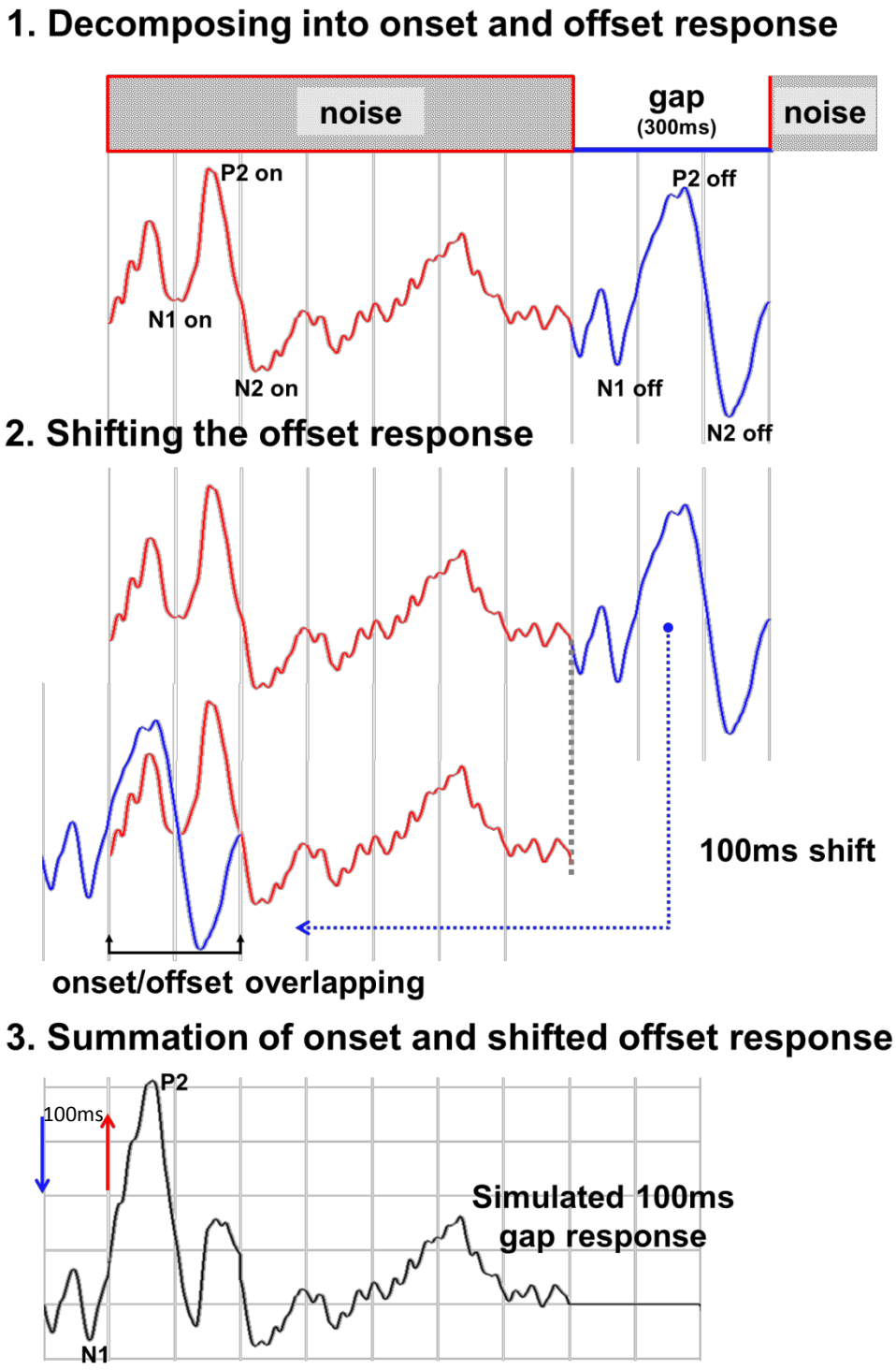


FIGURE 7.1. Schematic illustrates simulation of 100ms gap response using noise onset and offset responses of 300ms gap. The original 300ms gap response on the top is a filtered (1-30Hz) grand average response of 7 subjects. To simulate 100ms gap response, the offset response is shifted by 100ms as indicated in step 2. In step 3, the noise onset and the shifted noise offset are added to form the simulated 100ms gap responses. Noise onset (↑) and offset (↓) are indicated by arrows.

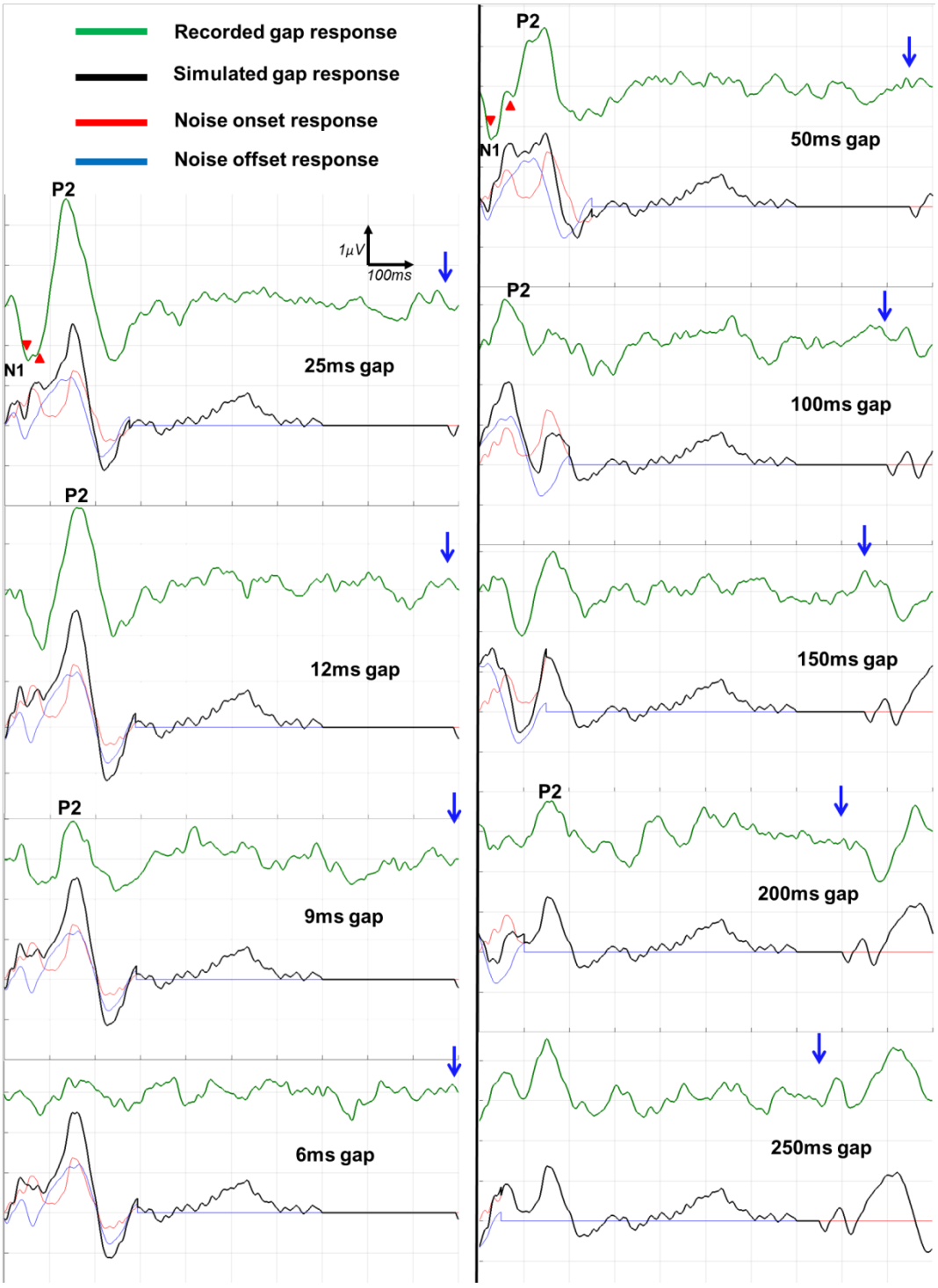


FIGURE 7.2. Recorded and simulated gap responses of 9 different gap durations. Simulated gap responses are constructed using noise onset and offset responses of 300ms gap. Noise offset is at *t*=0s, blue arrow (↓) indicates the location of noise offset.N1a and N1b sub peaks are marked by red triangles for 25 and 50ms gap responses.

N1 Morphology

Michalewski et al. (2005) and Pratt et al. (2005) have reported a bifid N1 when evoked by 20 or 50ms gaps. Pratt et al. (2007) suggested that the morphology of N1 is affected by the duration of the noise segment as well as the intensity of the noise. On the other hand, Palmer and Musiek (2013) did not observe the bifid N1 when the ear is stimulated with the same gap.

For the data presented above, a bifid N1 was observed for 25 and 50ms gaps. For both these gap responses, bifid N1 was present in 8 subjects out of 11. The main difference between the bifid N1 observed in our result and the one observed in Michalewski et al. (2005) and Pratt et al. (2005) studies is the latency between N1 sub peaks (N1a and N1b). They found that regardless of gap duration, the latency between N1a and N1b was 60ms, and they occurred at 90 and 150ms, respectively, as measured from the noise offset (gap onset) (Pratt et al., 2005). However, in our study we found that the latency between N1a and N1b associated strongly to the gap duration. For 25ms gap, the latency between N1a and N1b was 22ms. For 50ms gap, the latency between N1a and N1b was 52ms.

We suggest that the bifid N1 shape observed in the results and others is caused mainly by the overlapping of the onset and offset responses. Simulation of gap responses presented in Figure 7.2 demonstrated the possibility of a bifid N1 to be caused by the overlapping of the onset and offset responses (e.g. for the 50ms response). On the other hand, the bifid N1 observed in Michalewski and Pratt could be different from the bifid N1 observed in our results. Pratt et al.

(2007) suggest that the bifid N1 shape may be caused by the duration of the preceding noise segment. Their noise segment is 1500ms while our noise segment is 700ms preceding the gap. Additionally, Pratt et al. (2007) showed that the bifid N1 appears more prominently as the noise intensity increases. The noise level used in this dissertation was relatively low (70 dBSPL) compared to their noise intensity (90 dBSPL). In conclusion, their N1 is bifid with fixed latency between the sub peaks (60ms) because of a) the length of the noise segment, b) the higher intensity of the noise (90dBSPL). We did not observe the same bifid N1 because we stimulated with lower intensity (70dBSPL) and with shorter noise segment (700ms). However, we observed a bifid shape that is caused by the overlapping of the noise onset and offset as we showed earlier in the simulation section. The underlying mechanism of these discrepancies is, however, not known.

Another possible reason why the bifid N1 was not observed in all subjects may be attributed to the morphology of the onset or the offset response in each subject. The morphology of the onset and the offset responses are discussed more explicitly in the following section 7.3.

7.1.2 Early (ABR/MLR) Responses

The author is not aware of any gap in broadband noise studies to contrast our findings with. However, some magnetic encephalography studies have recorded AMLR to gaps in noise (Rupp et al., 2002; Rupp et al., 2004). They found that AMLR magnitude decreases as gap duration decreases. The results of experiment II support these findings. ABR-MLR responses elicited by

shorter gaps showed diminished ABR-MLR amplitude. Amplitude of these responses also decreases with shorter gap durations until the behavioral gap detection threshold (about 5ms) was reached.

The findings of Experiment II (using short gaps presented at 40Hz) showed a clear effect of gap duration on ABR/MLR responses (as shown in Figure. 6.5). Amplitudes of ABRs/MLRs diminished as gap duration decreased. Furthermore, peak amplitude reduced gradually until it subsided into residual EEG noise near 5ms, which is around the mean BGDT. The ABR/MLR responses to gaps in noise are confined to the interval 5-75ms, and are very consistent with the timing of activation of the brainstem and primary auditory cortex. The morphology of the 12ms gap response (Figure 6.5) is characterized by three negative peaks and three positive peaks; the positive peak around 20ms is the most prominent one. The latencies of the peaks are different to the ones elicited by clicks or tone-pips. However, peak latencies in our short gap responses were not affected by gap duration as shown in Figure 6.5.

7.1.3 Auditory Steady-State Responses

Two types of ASSRs were recorded in our experiments. The first one is ASSR, which is recorded using an isochronic 40Hz sequence. The second is QASSR, which is recorded using a low jittered 40Hz sequence. Figure 6.24 shows a comparison between ASSR and QASSR in time domain and frequency domain. In time domain, the shape of the 40Hz ASSR and QASSR was consistent with gap presentation rate (40 gaps per second). Furthermore, phasor analysis of ASSR and QASSR showed that both responses have similar phase

and magnitude distributions. Such degree of similarity between ASSR and QASSR validates the use of the CLAD method to extract gap-induced transient responses from QASSR (overlapping responses resulting from high rate stimulation, 40Hz).

The effect of gap duration on QASSRs was clearly observed in all subjects tested in experiment II. Reducing gap duration from 12ms to 0 showed a magnitude reduction as stimulation rate approaches the gap behavioral thresholds (about 5ms). The effect of gap duration on QASSR was consistent with effect of gap duration on ABR-MLR and LLR. Some researchers have developed objective gap detection methods using cortical gap responses (Michalewski et al., 2005; Palmer and Musiek, 2013; 2014; Pratt et al., 2005). The method that they have proposed is based on the existence of N1 or P2 components; they assign the gap detection threshold when cortical components are not observed in response to short gaps. However, in their proposed objective gap detection method, they judged the existence of cortical components subjectively. This lends interpretation of test results up to the test reviewer. Ideally, this type of classification test should be reviewer independent to avoid conflicting opinions about the existence of AEPs components. In clinical practice, it would be beneficial to have an objective test that can be performed in as reasonable time.

In experiment II, an objective gap detection method was proposed based on the analysis of QASSR. By adapting a quantitative analyzing method proposed earlier (Lachowska et al., 2012); we were able to obtain OGDTs. By

Contrasting the OGDTs and BGDTs obtained during this experiment, thresholds for the two methods were similar to within a 1ms difference in some cases as shown in Table 6.1. The mean OGDT (5.83ms) and the BGDT (5.83ms) indicates that this objective gap detection method could be used as a reliable objective method. However, further investigation in a larger population that includes patients with disorders related to temporal resolution is needed.

7.2 Rate Effect

One of the aims of this dissertation was to investigate the effect of stimulation rate on gap responses. Studying the effect of rate on gap responses may expand the understanding of how various AEP components vary with stimulation rate. It has been shown that MLR and LLR components are sensitive to the rate of stimulation (Azzena et al., 1995; Holt & Ozdamar, 2015; Ozdamar et al., 2007). However; these studies were typically conducted using acoustic clicks or swept tones. In our study, the feasibility of recording gap in noise stimulus responses at 40, 5, 1 and 0.5Hz was investigated. In order to record gaps responses, we used a single gap duration (12ms) to evoke AEPs at different rates. Although we found 25ms gap presented at 1Hz elicited the largest N1-P2 amplitude, we employed 12ms gap since it elicited a more well defined peaks in the ABR-MLR region. Additionally, when stimulating at a high rate (40Hz), there is a limit for the ratio of number of noise segments to the gap (gaps were presented every 25.6ms, see Figure 4.2). The 40Hz stimulation rate precluded the use of 25ms gap due to its size.

The following sections discuss the existence of ABR, MLR, and LLR components in all rate responses.

7.2.1 Cortical Responses

Cortical components were clearly observed at low stimulation rates (e.g. 12ms gap responses in Figure 6.25). The N1 and P2 were clearly identifiable in 0.5Hz and 1Hz responses. The N1-P2 amplitude was not significantly different between 0.5 and 1Hz rate responses. Additionally, N1 and P2 latencies were not significantly affected by rate ($p>0.05$). The 12ms N1 and P2 components were fairly similar to the cortical components reported in Harris et al. (2012).

For 0.5Hz and 1Hz responses, a consistent positive peak at 50ms latency from noise offset was observed (Figure 6.25). A small positive deflection around 70ms latency was also observed. We believe that the peaks observed at 50ms latency could be Pa and the peak observed at 70ms latency is Pb; therefore we labeled them accordingly in the figure. However, Harris et al. (2012) did not report observing P(50) or P1.

Pa was the most resilient peak across all stimulation rates (0.5, 1, 5, and 40Hz). Pa was observed in all subject responses as shown in Table 6.2. The mean latency of Pa was stable in low rates (48ms for 0.5, 1, 5Hz) and significantly earlier (44ms) at 40Hz. Pb was only observed in 30% of the subjects at 0.5Hz. For higher rates (5Hz and 40Hz), late components N1 and P2 were not detectable due to adaptation, as anticipated.

7.2.2 Early (ABR/MLR) Responses

Wave V has been observed for gap-evoked responses when the gap is longer than 3ms (Poth et al., 2001; Werner et al., 2001). It has been shown in both studies that wave V latency is corresponding to the noise onset. Poth et al. (2001) found that wave V amplitude decreased as the gap duration decreased. Werner et al. (2001) obtained gap detection thresholds based on the absence of wave V.

In experiment VI, a positive peak with mean latency of 12ms from noise onset was observed; we believe that this positive peak is corresponds to the conventional wave V. It was observed in rate responses of 1, 5 and 40Hz and not identifiable in most of the subjects for 0.5Hz responses (see Figures 6.25 and 6.26). Wave V latency exhibited no significant change at 5 and 1Hz rates. At 40Hz, wave V mean latency was significantly earlier (10ms from noise onset) than 5 and 1Hz responses. Based on the latencies across rates we believe that wave V is generated mainly by the noise onset.

As shown in Figure 6.25, the ABR/MLR was characterized by the following peaks: V, Na, Pa, Nb and Pb. Pa was the most consistent peak across all rates. Pa was significantly earlier at 40Hz ((40Hz: 44.8ms) vs (5Hz: 47.0ms), (1Hz: 47.7ms) and (0.5Hz: 49.2)). It was noticed in the grand average responses that Na-Pa amplitude increased as the rate decreased, while Nb-Pb amplitude decreased with rate. These observations suggest that Pa and Pb amplitudes are sensitive to stimulation rate.

7.3 Onset / Offset Responses to Long Gaps

Michalewski et al. (2005) and Pratt et al. (2005) reported the existence of two separate onset and offset responses for long gaps (e.g. 500ms). Michalewski et al. (2005) showed that noise offset N1 response has a bifid wave shape. They also showed that offset N1 wave was broader, unlike the sharp N1 wave shape for the onset condition. The responses that they showed were only the average of two normal subjects with good SNR signals. They characterized offset responses by the presence of N1 and P2 peaks. Also, they did not report observing P1 in the offset response but did observe it in response to noise onset only (Pratt et al., 2007).

The 300 and 250ms gaps elicited two distinct responses as seen in experiments III, IV and V. The grand averaged noise onset response in Figure 6.20 showed the following peaks: V (with an average latency of 10ms), Pa (33ms), P1 (57ms), N1 (110ms), P2 (150ms) and N2 (225ms). The observed peaks in the offset response were only P1 (50ms), N1 (74ms), P2 (170ms) and N2 (235ms). Unlike Pratt et al. (2007), the presented results showed the presence of P1 in both the onset and the offset responses. We also observed ABR-MLR components to noise onset, but peak V and Pa were not identifiable in averaged noise offset responses.

In experiment V, the 300ms gap responses were compared with two clicks separated by 300ms. The morphology of the 1st and the 2nd click responses were similar, which was anticipated due to the identical repeated stimulus. However, in the 2nd click response, P1 was fairly diminished. The

reduction effect on P1 may account for the residual cortical components of the 1st click; however this claim needs to be verified by further investigation. The onset and offset responses to the gap-in-noise stimulus showed marked dissimilarity (see Figure 6.19). We suspect a similar effect of the residual late (after 250ms) cortical wave of the onset response. As observed in Figure 6.19, the onset response seems to be carried on a slow positive wave.

Responses to click and noise onset conditions were very similar in morphology with following peaks being clearly visible in both recordings: V, Pa, P1, N1, P2, and N2. However, for noise onset, wave V latency was 10ms, and 8ms for click responses. The same delay (2ms) was observed in Pa and P1 in contrast with click responses. This suggests that the delay in the ABR and MLR components of noise onset could be caused by one or both of the following factors: a) The transition from noise to gap or from gap to noise was not abrupt and the silent gap was gated with a slope of 1ms on either side, b) the suppressing effect of noise masking on ABR and MLR components (Ozdamar & Bohorquez, 2008).

The noise offset response was different from that of noise onset and click conditions. Although noise offset response was characterized by peaks P1, N1, and P2, the latencies of these peaks were not similar to the noise onset. The latency of P1 for noise offset was 45ms, which was significantly earlier than P1 onset 57ms (see Figure 6.22). Also, P1 offset was broad, unlike the sharp P1 during onset. Also, a small positive peak at 24ms latency was observed.

Additionally, ABR components were not observed for noise offset responses, instead, only a negative peak peaking at 12ms was observed.

7.4 Filtering and Averaging Effects on AEPs

For prior literature, most cortical gap response studies utilized a bandpass filter of (1-30Hz) or narrower (Harris et al., 2012; Michalewski et al., 2005; Palmer and Musiek, 2013; Pratt et al., 2005). In these studies, the authors reported that P1 is absent or greatly reduced. However, our results showed a consistent positive peak around 50ms latency in response to 12ms gap. We believe that the absence of P1 in their studies is caused by the harsh use of the (1-30Hz) filter. Filtrating may greatly reduce the amplitude of the ABR-MLR components (before 70ms).

In order to demonstrate the effects of filtering on AEP components, several different filters were applied to the same traces that have ABR, MLR or LLR components. The preset acquisition filter for the results presented in this dissertation was broadband (1-1500Hz). The additional digital filters used for demonstration are (1-30Hz), (30-1500), and (100-1500) as illustrated in Figure 7.3. Filters were 2^{nd} order zero-phase Butterworth filters (6dB/oct). As shown in the figure, applying a 1-30 Hz filter greatly reduces waves V and Pa amplitudes, and removes Pb. On the other hand, as expected, applying (30-1500 Hz) preserved the early components and eliminated the cortical components. The 100-1500 Hz filter severely diminished all AEP components. The demonstration of these four digital filters showed severe effect of the filtrating on the appearance and interpretation of AEP components. Since P1 is very sensitive to

filter settings, it is recommended that researchers should carefully choose appropriate digital filters before reporting the absence of P1.

In this study, the P1 was observed in both the onset and the offset responses. Pratt et al. (2008) reported the presence of P1 to noise onset but not for noise offset. Pratt et al. (2008) used a low pass filter of 24Hz. It is suspected that P1 to offset was reduced or eliminated by the low pass filter. In Figure 7.4, the effect of the 1-30Hz filter on grand average and individual subject responses are shown.

Another factor that influences the presence or the amplitude of AEP components is the number of sweeps averaged. In this study, the mean number of sweeps averaged to obtain AEP responses is 500 sweeps. Pratt et al. (2008) averaged 100 sweeps while Michalewski et al. (2005) averaged only 50 sweeps at 0.5 gap/sec. Figure 7.4 compares the effect of numbers of averaged sweeps for the average of 11 subjects (top, red) and for a single subject GAP017 (lower, blue), The right panel shows an average containing 500 sweeps, and the left panel shows averaging 100 sweeps. Additionally, (1-30Hz) filter was applied to all the four traces in Figure 7.4 (black lines). The lower number of sweeps and low bandwidth filters may greatly alter AEP components in the first 70ms, which includes P1. For the 500 sweep averaged traces, more distinct ABR, MLR LLR components are visible due to the reduction of the residual noise (increased SNR). However, increasing number of sweeps appears to slightly reduce the amplitude of the cortical responses. The reduction of amplitude as the number of sweeps increased may be attributed to the adaptation effect.

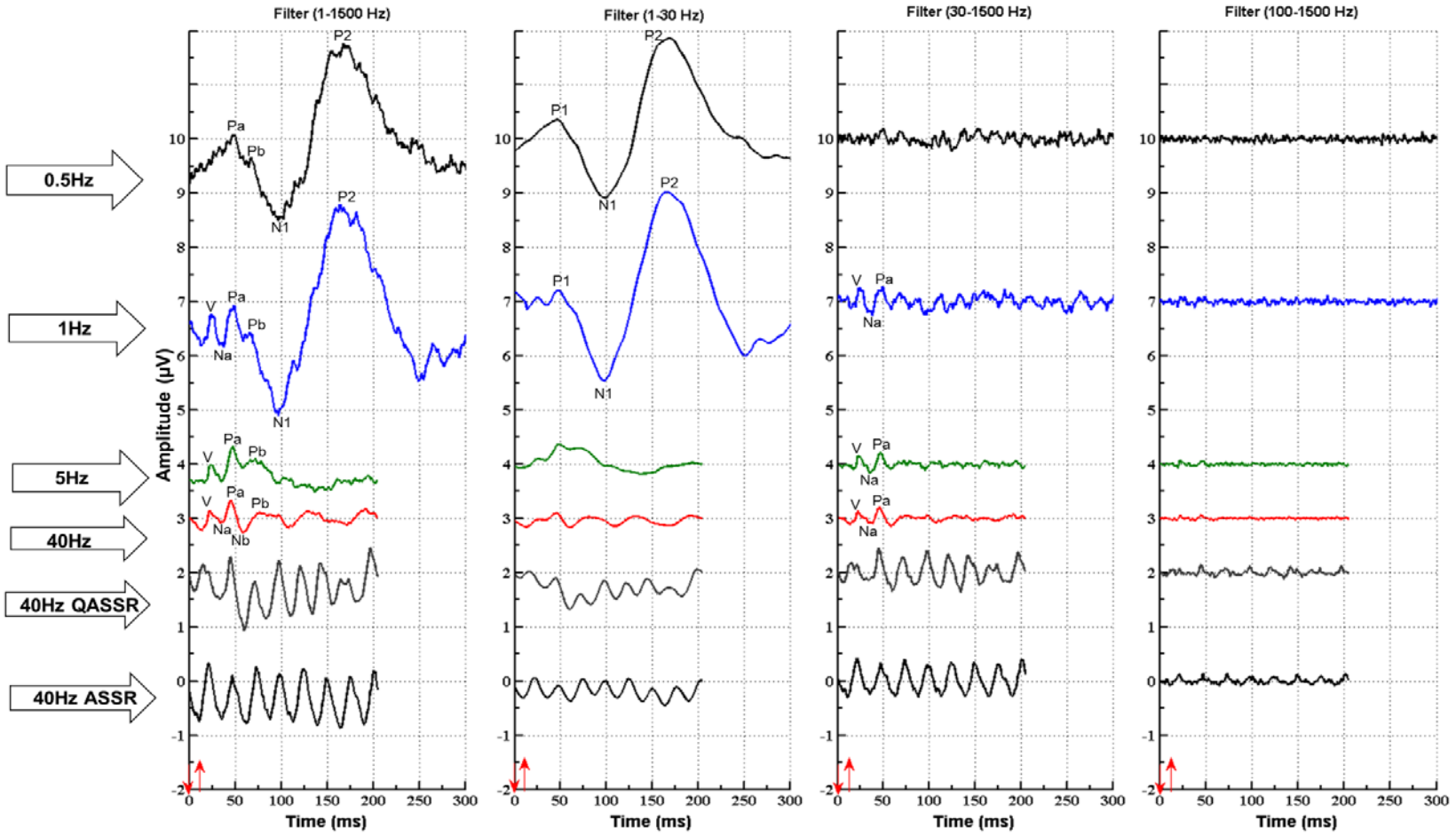


FIGURE 7.3. Grand average responses for 12ms gap used to illustrate the filtration effect on AEP components. left panel shows traces with preset filter (1-1500Hz). The 2nd panel shows the effect (1-30Hz) filter on ABR and MLR peaks. The 3rd panel shows the effect (30-1500Hz) filter on LLR peaks. The right panel shows the effect (100-1500Hz) filter on LLR peaks. 12ms gap is indicated temporally by the red arrows, noise onset (↑) and offset

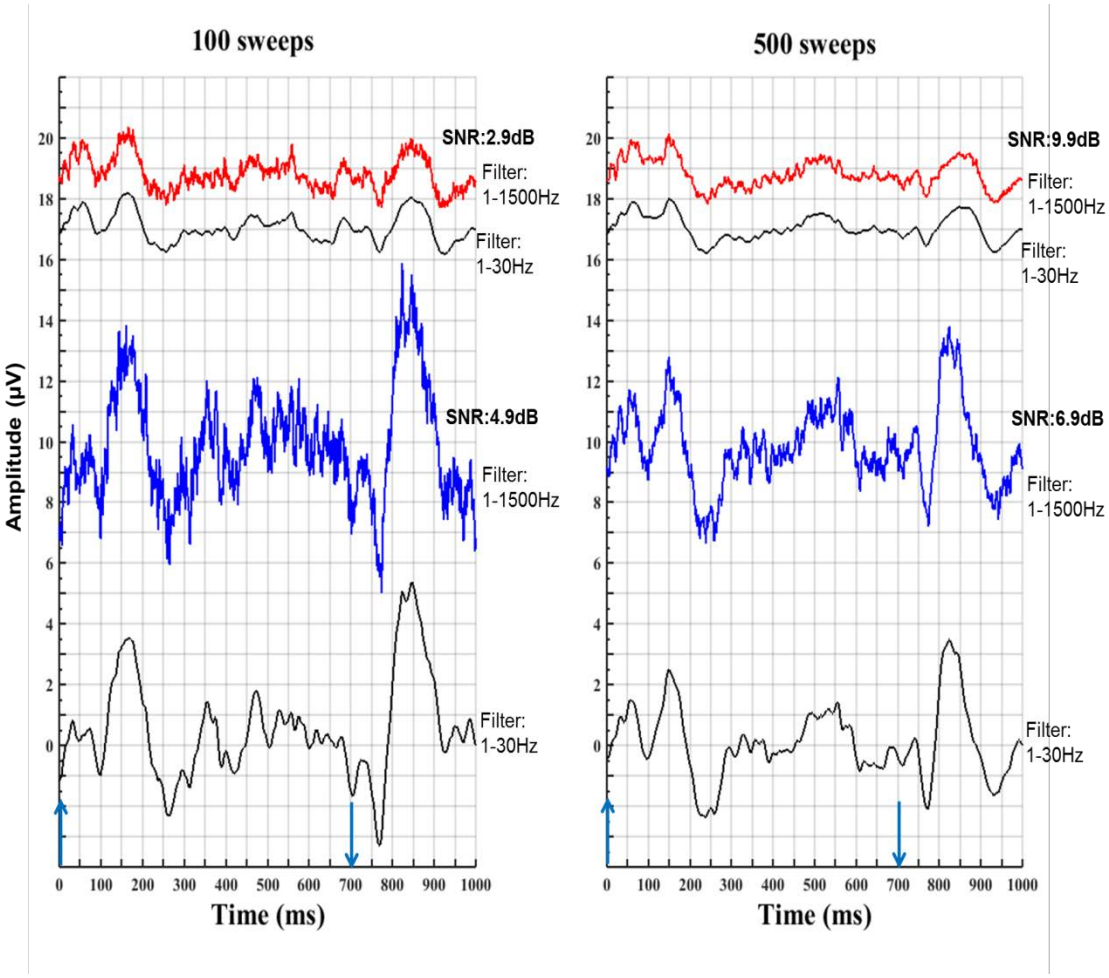


FIGURE 7.4. 300ms gap responses showing the effects of sweep number and filtering on AEP components. The left panel shows traces averaged wtih 100 sweeps. The right panel shows traces averaged with 500 sweeps. Red traces are grand average of 11 subjects. Blue trace is an individual subject trace (GAP017). Black traces are band pass filtered to (1-30Hz). SNR and Filter cut-off points are shown next to each trace. Arrows are used to indicate the temporal location of noise onset (↑) and offset (↓).

7.5 Conclusion

This dissertation examined human auditory evoked potentials (AEP) evoked in response to gaps in broadband noise. Evaluation of AEPs focused on three aspects: 1) acquiring auditory response profile across different stimulation rates (0.5-40 Hz) under uniform recording parameters containing components from ABR, MLR LLR and ASSR; 2) recoding AEPs to short, medium and long gaps to assess the effect of gap duration on AEPs components; and 3) to investigate the influence of noise onset/offset on the transient evoked responses.

Recording gap responses across different presentation rates showed that the 1Hz stimulation rate was optimal for acquiring all ABR, MLR, and LLR components were observed simultaneously. For 0.5Hz, only late latency components were observed, while for 5 and 40Hz evoked only ABR-MLR (no LLRs). For 1, 5 and 40Hz rate recordings, ABR-MLR components (V, Na, Pa, Nb and Pb) were present in in response to 12ms gap and can be reliably identified (for individual subject averages). For all rates acquired using the 12ms gap (0.5, 1, 5, 40Hz), Pa was the most resilient peak observed at 48ms average latency.

The 40Hz QASSR measurements of magnitude and phase showed very good agreement to conventional ASSRs. This high degree of agreement between ASSR and QASSR validates the use of the CLAD method to extract gap-induced transient responses from the QASSR. Therefore, the 40Hz QASSR could be used to objectively evaluate gap detection thresholds in normal hearing individuals.

For short gaps (<25ms), several studies have reported a reduction in amplitudes of cortical responses as the gap becomes shorter (Harris et al., 2012;

Michalewski et al., 2005; Palmer and Musiek, 2013; Pratt et al., 2005). Results of this study confirmed the reduction of cortical component amplitudes as gap duration decreased. Additionally, ABR-MLR component amplitudes diminished as gap duration decreased. Also, QASSR amplitudes were reduced as the gap became shorter. The phenomenon of amplitude reduction as gap becomes shorter is observed only for short gaps (25ms or shorter).

The 12ms gap evoked well-defined ABR, MLR and LLR components. The 25ms gap response was characterized by the largest N1-P2 amplitude across all gap durations. It is suggested that when the separation between the onset and the offset of the noise is 25ms, the overlapping of onset and offset responses is mostly constructive. Additionally, when the separation between adjacent gaps is longer than 25ms, the overlapping effect becomes less constructive and more destructive. Medium gaps (longer than 25ms) were affected by the destructive overlapping of noise onset and offset. Simulations of the gap responses using isolated noise offset and onset responses clarified and supported the hypothesis of the overlap on gap responses is the result of simple superposition. The simulated gap responses were comparable to recorded gap responses.

Longer gaps (250 and 300ms) showed two distinct responses (to gap onset and offset). For the 300ms gap, the response to noise onset was characterized by the following peaks: V, Pa, P1, N1, P2 and N2, and noise offset response was characterized by P1, N1, P2 and N2. Peak V and Pa were not identifiable for noise offset responses. Also, component latencies to noise offset responses were not similar to noise onset.

Appendix

A. Sample Size

This work includes six experiments that have different sample size varying between 6 and 14 subjects as seen in Table 4.1. In this section, we will justify the number of subjects recruited. The quantification is based on the quality change of the electrophysiological response as sample size changes. AEPs were the common variable recorded across experiments and, they are the main focus of the dissertation. We believe that sample size as low as six subjects can be considered sufficient to some extent. However, to support the claim we are providing the statistical analysis in this section.

Initially, we started the analysis by assuming that 14 subjects is enough number of subjects based on qualitative observations that showed no drastic changes in AEPs when the number of subjects decreases by half. Based on this assumption, we picked one variable from one rate responses to use it in the statistical analysis. One of the responses used in this dissertation is 0.5Hz response. From 0.5Hz response we picked N1-P2 amplitude as the variable in the sample size statistical analysis. Three different approaches were utilized to quantify the number of subjects (sample size):

1. Quantifying the change in the mean, standard deviation and standard error as we exclude more subjects randomly.
2. Implementing confidence intervals of 80% to measure the change in margin of error as the sample size decreases.

3. Comparing the grand average response when fewer samples are averaged.

A.1 Descriptive Statistics and t-test

AEPs were recorded from 14 subjects in response to 0.5, 1, 5 and 40 Hz noise gaps. However, in this section we are only quantifying the change in N1-P2 amplitude in response to noise gaps presented at rate of 0.5Hz. In Table A.1, the mean, standard deviation and standard error were calculated for 14 subjects. Then, samples were picked randomly to form subsamples ranging from 2 subjects up to 14 (As seen in Table A.1). Mean, standard deviation, and standard error were calculated for each subsample. The change of mean and standard error as a function of sample size number of subjects is shown in Figure A.1.

TABLE A.1. N1-P2 amplitude values are listed for 14 subjects in the first column. Sample size decrease by randomly excluding subjects from the mean. Standard deviation and standard error are calculated for each sub

	Number of subjects												
	14	13	12	11	10	9	8	7	6	5	4	3	2
N1-P2 amplitude (μV)	5.29	2.52	3.99	2.52	3.99	5.29	3.99	4.38	5.29	2.52	3.97	2.43	3.72
	2.43	4.23	3.71	4.23	5.29	2.43	7.15	7.15	4.38	4.23	7.15	5.29	7.15
	4.23	5.29	4.26	5.29	4.26	7.15	3.72	4.29	4.23	4.38	3.99	3.99	
	3.97	2.43	5.29	4.38	2.52	4.29	4.38	2.52	4.26	5.29	5.29		
	3.71	5.29	5.29	6.82	4.23	4.38	4.29	6.82	6.82	3.99			
	5.29	4.29	2.52	4.26	7.15	6.82	5.29	2.43	3.71				
	4.26	3.97	3.72	3.97	6.82	3.72	3.97	5.29					
	4.38	3.72	4.29	3.72	5.29	5.29	5.29						
	3.99	3.99	4.38	2.43	3.72	3.71							
	7.15	4.38	3.97	4.29	3.71								
	2.52	7.15	7.15	7.15									
	6.82	6.82	6.82										
	4.29	3.71											
	3.72												
Mean	4.43	4.45	4.62	4.46	4.70	4.79	4.76	4.70	4.78	4.08	5.10	3.90	5.44
St.Dev	1.35	1.41	1.32	1.49	1.45	1.52	1.13	1.87	1.12	1.00	1.50	1.43	2.43
St.error	0.36	0.39	0.38	0.45	0.46	0.51	0.40	0.71	0.46	0.45	0.75	0.83	1.72

As shown in Figure A.1 mean amplitude of N1-P2 is fairly steady as the number of subjects decreases. However, when the number of samples is less than 5 subjects, the mean and the standard error start deteriorating. Based on this observation, we have used data analysis tool in Microsoft excel to conduct a t-test comparing the mean of 14 and 6 subjects as shown in Table A.2.

We compared the mean of 14 and 6 subjects having P-value of 0.05. Table A.2 shows t-test results that reveals no significant difference in the mean between 14 and 6 subjects.

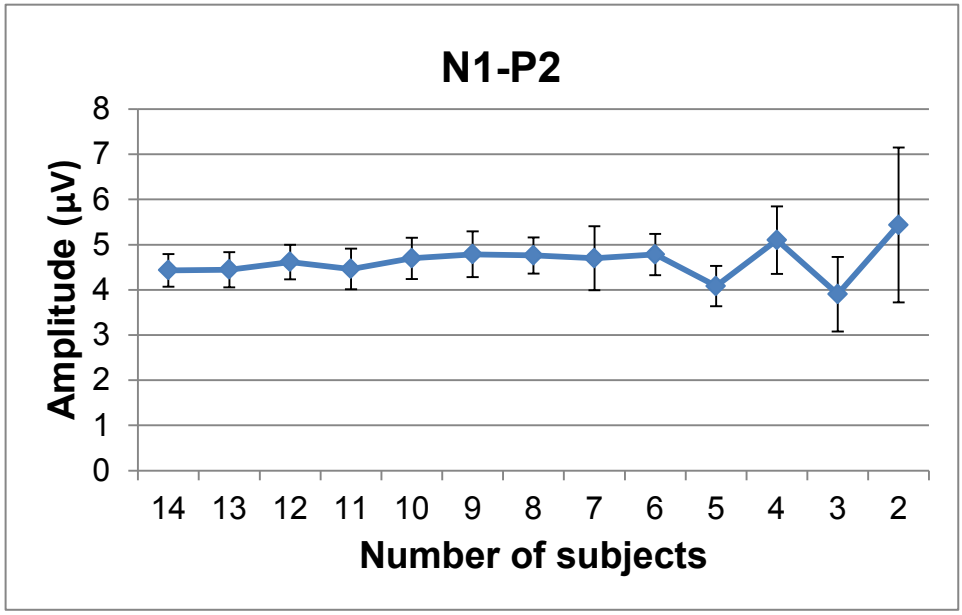


FIGURE A.1. Mean and standard error bars are plotted for N1-P2 amplitude as function of sample size.

TABLE A.2. T-Test: Two-Sample Assuming Equal Variances

Number of subjects	*14*	*6*
Mean	4.432143	4.781666667
Variance	1.827418	1.259896667
Observations	14	6
Pooled Variance	1.669773	
Hypothesized Mean Difference	0	
df	18	
t Stat	-0.554335	
P(T<=t) one-tail	0.293086	
t Critical one-tail	1.734064	
P(T<=t) two-tail	0.586171	
t Critical two-tail	2.100922	

A.2 Margin of Error

In this section, we assumed that sample size of 14 subjects is sufficient sample size. Therefore, we used the following equation to estimate the margin of error of different sample size based on confidence interval of 80%:

$$\mathrm{ME} = \mathbf{Z\alpha/2} * \boldsymbol{\sigma}/\sqrt{\mathbf{n}}$$

- **Zα/2**: Confidence coefficient is 1.29 (80% confidence intervals)
- **σ**: Standard deviation:1.35
- **ME**: Margin of Error: showed in Table A.3
- **n**: Sample size

TABLE A.3. Margin of error Values of calculated based on the sample size. Rate of change is calculated for margin of error.

sample size (n)	Margin of Error (ME)	Rate of change in (ME)
14	0.47	
13	0.48	0.02
12	0.50	0.02
11	0.53	0.02
10	0.55	0.03
9	0.58	0.03
8	0.62	0.04
7	0.66	0.04
6	0.71	0.05
5	0.78	0.07
4	0.87	0.09
3	1.01	0.13
2	1.23	0.23

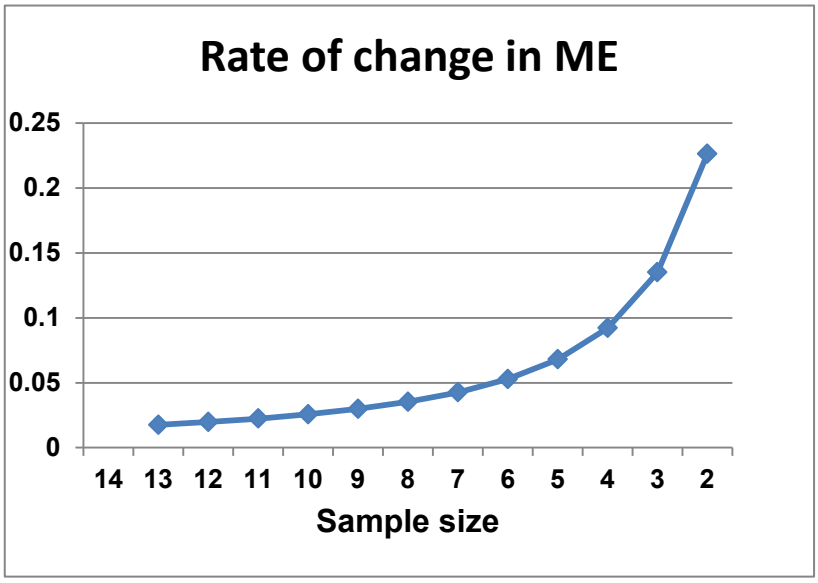


FIGURE A.2. Rate of change of the margin of error plotted as a function of sample size.

A.3 Qualitative Analysis

Based on the random selection of subsamples in Table A.1, we plotted the grand average traces of each subsample. Figure A.3 shows AEPs elicited by 0.5Hz gap stimuli. In Figure A.3, the top trace shows AEPs averaged of 2 subjects selected randomly, and then the number of subjects increases until reaching the grand average of all the 14 subjects.

Correlation coefficients (R) between grand average trace of 14 subjects with all subsamples averages are shown in Table A.4. R values were calculated using the following function in MATLAB:

R = corrcoef(Ave14,Ave6);

As observed in the Table there is strong correlation with lower number of subjects (as low as 4 subjects).

A.4 Conclusion

The statistical analyses showed steady mean N1-P2 amplitude for sample size as low as five subjects. Additionally, the rate of change of margin of error was steady until sample size reached 5 or 6 subjects. Also, the qualitative analysis of the signal using the correlation factor, showed that sample size of 4 subjects or more is highly correlated to the 14 subjects. All these accumulative findings led us to assume that sample size as low as 6 subject is sufficient. However, larger sample size would improve the reliability of any study.

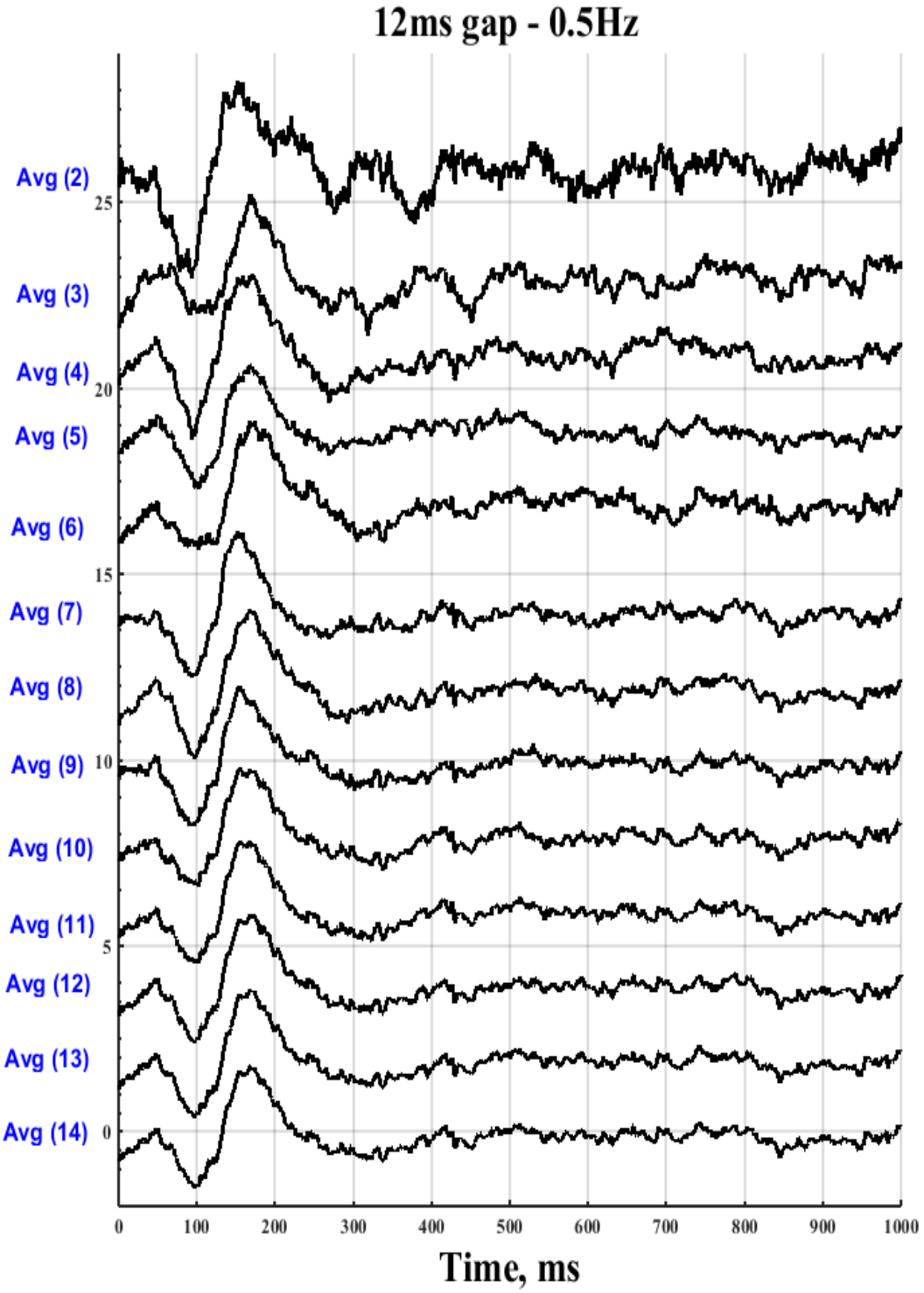
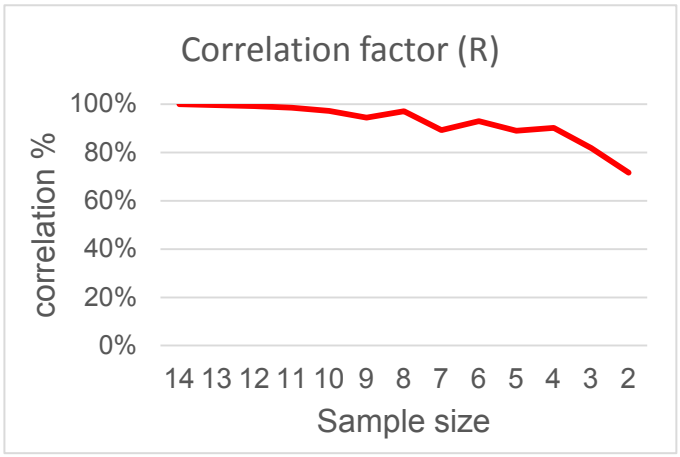


FIGURE A.3. Grand average traces of 0.5Hz response. The bottom trace is the average of 14 subjects. The number of subjects decreased from 14 to 2 subjects in the top trace.



Sample size	(R) values
14	1
13	0.9964
12	0.9923
11	0.9849
10	0.9724
9	0.9447
8	0.9711
7	0.893
6	0.9301
5	0.8903
4	0.902
3	0.819
2	0.717

FIGURE A.4. Values of the correlation factor (R) are shown in the table on the right. On the left, the correlation factor plotted as a function of the sample size.

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